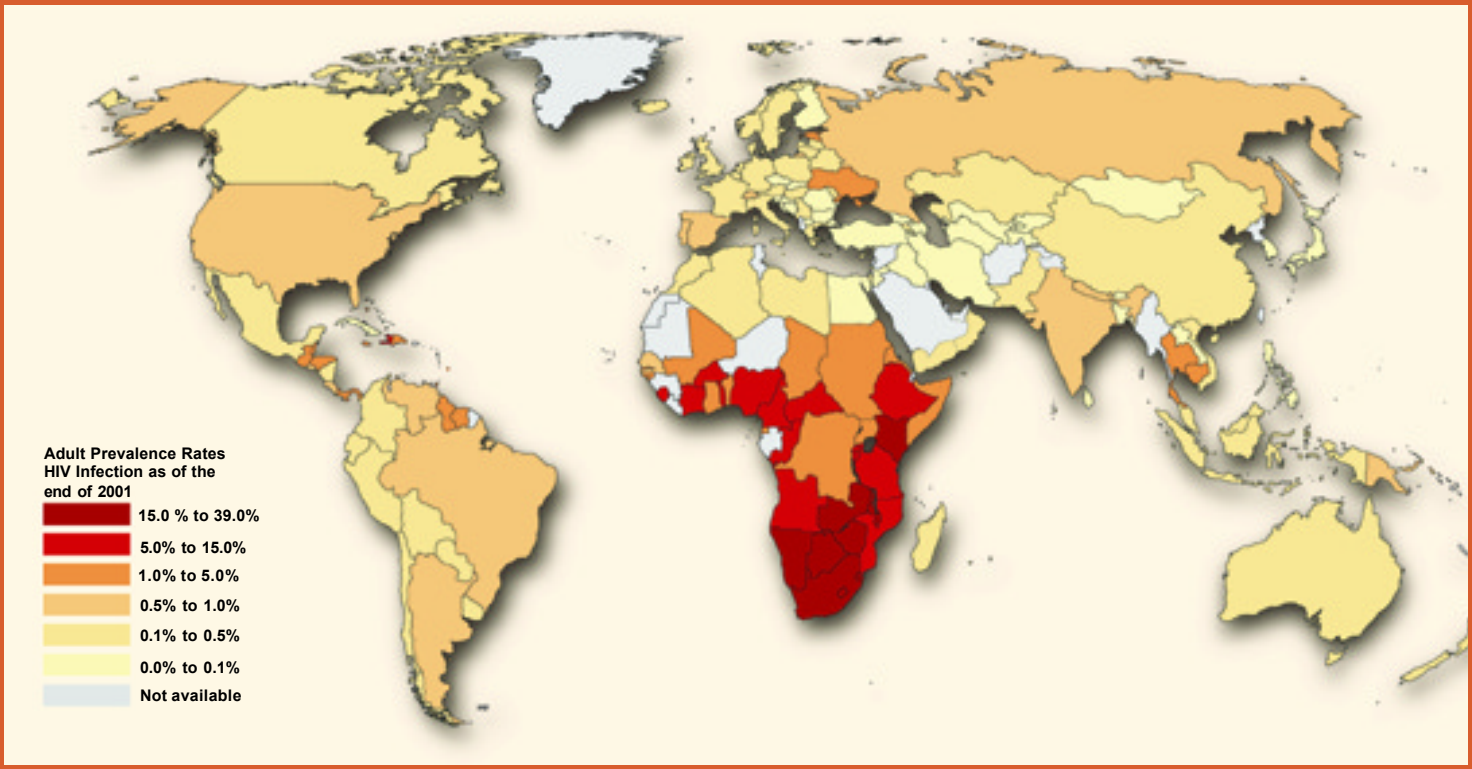
Pediatric, Adolescent, and Maternal AIDS Branch NICHD



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EXECUTIVE SUMMARY

This represents the third report of the Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), part of the Center for Research for Mothers and Children (CRMC) at the National Institute of Child Health and Human Development (NICHD), to the National Advisory Child Health and Human Development (NACHHD) Council. Since its inception in 1988, the Branch has supported and conducted epidemiologic, biomedical, and bio-behavioral research in the areas of HIV infection and disease in mothers, women of reproductive age, infants, children, adolescents, and families.

This is a critical time for women and children, in terms of HIV infection research. Scientists have made substantial advances in understanding the pathogenesis of HIV infection, and in the treatment and monitoring of HIV disease. These advances formed the basis for recommending potent combination antiretroviral therapeutic regimens that maximally suppress viral replication, and that are associated with significant reductions in HIV-related morbidity and mortality. However, as with research in many other diseases, studies in children have lagged behind those in adults, and gender differences often go unappreciated. Additionally, in developing countries the burden of new infections is increasingly falling on young women, with a continuing increase in the number of children newly infected via mother-to-child transmission, as well as the skyrocketing number of AIDS orphans.

Although the pathogenesis of HIV infection is similar for all HIV-infected persons, there are unique considerations for HIV-infected infants, children, adolescents, and women that warrant research specifically focused on these populations, including:

- The effect of HIV infection on pregnancy and the fetus;
- The impact of pregnancy on HIV therapy, especially in regard to antiretroviral drug use in pregnant women, including the potential need for dosing alterations, differing susceptibility to certain drug toxicities, and the effect of drugs on the fetus and infant;
- Acquisition of HIV infection through *in utero*, intrapartum, or postnatal exposure (via breast milk) for most HIV-infected children;
- Potential long-term effects of *in utero* exposure to zidovudine (ZDV) and other antiretroviral drugs used for prevention of perinatal transmission;
- Differences in the diagnostic evaluation of perinatal infection due to the persistence of transplacental maternal antibody in the infant until age 15 to 18 months, rendering the HIV antibody test insufficient for diagnosis in this age group;
- Differences in immune function and markers (such as $CD4^+$ lymphocyte count) between young children and older children and adults;
- Age-related changes in pharmacokinetic parameters caused by continued development and maturation of organ systems involved in drug metabolism and clearance, which may result in changing drug levels, as well as by different manifestations of drug toxicity in children;
- Differences in the clinical and virologic manifestations of perinatal HIV infection and HIV-associated opportunistic infection, due to acquisition of infection at a time of immunologic immaturity;
- Special considerations associated with adherence to therapy for children and adolescents; and

- Gender differences in immunologic and virologic parameters of HIV disease and the gender-specific clinical manifestations of infection with HIV (e.g., cervical cancer).

The mission of the Branch is to support and conduct research into the epidemiology, natural history, pathogenesis, transmission, and treatment of HIV infection and disease in infants, children, adolescents, pregnant women, mothers, women of childbearing age, and the family unit as a whole. To that end, PAMAB and PAMAB-funded researchers have made substantial contributions to domestic and international research in pediatric and maternal HIV/AIDS (as illustrated in the Research Advances section of this report).

In 1999, the NACHHD Council recommended that PAMAB increase its focus on international HIV activities, and on HIV-related issues in adolescents. During the past four years, the Branch has significantly expanded its international HIV research, including the following efforts: enhancements in the investigator-initiated, international grant portfolio; expansion of the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network to include six international clinical trials sites; PAMAB participation in the development and conduct of perinatal trials in developing countries through the NICHD co-funded HIV Prevention Trials Network (HPTN); PAMAB support for the International, Clinical, Operational, and Health Services Research Training for AIDS and Tuberculosis (ICHORTA-AIDS/TB); joint support of a new initiative on prevention of breastfeeding transmission in Africa with the Centers for Disease Control and Prevention (CDC); and the incorporation of new international projects into the NICHD Domestic and International Pediatric and Pediatric HIV Studies Network aimed at training, infrastructure development, and the conduct of trials in Latin America, the Caribbean, and India.

The Branch has also expanded its adolescent activities. PAMAB has shifted from funding the observational Adolescent Medicine HIV/AIDS Research Network (AMHARN), to creating and funding the interventional Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions that will investigate primary prevention (including HIV vaccines) in at-risk youth, as well as clinical management and antiretroviral therapy of HIV-infected adolescents.

This report outlines the major initiatives of the Branch and highlights recent scientific advances from PAMAB-supported research.

BACKGROUND: THE CONTINUED IMPACT OF HIV ON CHILDREN, ADOLESCENTS, AND WOMEN

Following the results of PACTG 076 in 1994, which demonstrated that antiretroviral prophylaxis of HIV-infected women and infants could decrease mother-to-child transmission by nearly 70 percent, scientists have made dramatic advances in decreasing perinatal HIV transmission in developed countries. Currently, enhanced prenatal HIV counseling and testing, coupled with use of highly active antiretroviral therapy (HAART) by pregnant women for treatment of their HIV disease and for prevention of transmission, and increased rates of elective cesarean delivery have

lowered perinatal transmission rates to 1 percent to 2 percent in the United States. About 6,000 HIV-infected women give birth each year in this country; it is estimated that the number of infants in the United States who acquire HIV infection through mother-to-child transmission has decreased from 2,000 per year prior to 1994, to less than 400 annually at the present time.

However, a number of barriers to eliminating perinatal HIV infection in the United States remain, including: a continued increase in HIV transmission to women, particularly adolescents, in whom high rates of unintended pregnancies also exist; lack of prenatal care, particularly among women at high risk for HIV infection, such as women using illicit drugs; and a failure to identify HIV infection during pregnancy. Particularly problematic is prevention of transmission in infants born to women whose HIV infection is unrecognized until they give birth, which means they have received neither antiretroviral prophylaxis, nor elective cesarean delivery. Interventions are needed that can reduce transmission under such circumstances, including evaluation of the feasibility of rapid HIV antibody testing during labor, and identification of optimal post-exposure antiretroviral prophylaxis regimens.

While the number of infected children born annually in the United States has dramatically decreased, large numbers of children who are uninfected are exposed to antiretroviral drugs (most often multiple drugs) *in utero*; therefore, more information is needed about potential short- and long-term toxicities of such exposures. One study has suggested rare occurrence of significant mitochondrial toxicity in HIV-exposed, but uninfected, infants with *in utero* antiretroviral exposure, although a causal relationship has not been definitively established. Nucleoside analogue antiretroviral drugs, such as ZDV, can be incorporated into cellular DNA and are mutagenic *in vitro*, which raises the potential concern for carcinogenicity. Research is needed to define and evaluate the short- and long-term effects of *in utero* and neonatal antiretroviral exposure in children born to HIV-infected women.

In the United States, an estimated 10,000 to 15,000 children under the age of 13 are living with HIV infection, most of whom have not yet developed AIDS. Clinical trials of antiretroviral treatment conducted by the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network, in collaboration with the Pediatric AIDS Clinical Trials Group (PACTG) funded by the National Institute of Allergy and Infectious Diseases (NIAID), have led to incremental improvements in the health of HIV-infected children. Based on the results of these trials, current standard treatment for HIV-infected children is combination therapy with HAART. The late outcomes follow-up protocol PACTG 219 has documented a significant decrease in mortality in infected children, concomitant with an increased use of combination therapy containing protease inhibitors.

In the era of HAART, the manifestations of HIV disease in children have shifted. Prospective cohort studies such as the Women and Infants Transmission Study (WITS) have documented fewer AIDS-defining opportunistic infections and secondary infectious complications in infected children, but noted an increasing number of children with chronic, subtle neuropsychologic and neurodevelopmental dysfunction and growth disturbances.

As HIV becomes a chronic disease in children, research questions have shifted to evaluating the impact of HIV infection and HAART on growth, sexual maturation, metabolism, and neurodevelopment and neurologic function. Additionally, as scientists increasingly recognize long-term adverse outcomes of antiretroviral therapies in adults, such as lipodystrophy, insulin resistance, and disorders of bone metabolism, evaluation of the long-term effects of therapy in children, for whom life-long therapy will be required, is essential. Many questions also remain related to treatment management in children, as well as important basic science questions about the role of the immune system and evolution of the virus for the control of HIV infection in children.

In contrast to perinatal infection, the HIV epidemic among adolescents has remained unchecked. It is estimated that 25 percent of all new cases of HIV infection in the United States occurs in adolescents age 13 to 19 years, with half of the infections identified in persons under age 24. Surveillance data indicate that new infections among adolescent females equal or surpass new cases in adolescent males. Heterosexual transmission is the predominant mode of HIV acquisition in adolescent females, while homosexual transmission accounts for an increasing number of cases in adolescent males. Of the new infections, 62 percent occur in 13- to 24-year-old youth of African American or Hispanic origin. It is estimated that 12,000 to 38,000 youth, age 13 to 19, and 62,000 to 185,000 older youth, age 19 to 24, are currently HIV-infected in the United States. Additionally, increasing numbers of children who were infected perinatally are surviving into adolescence.

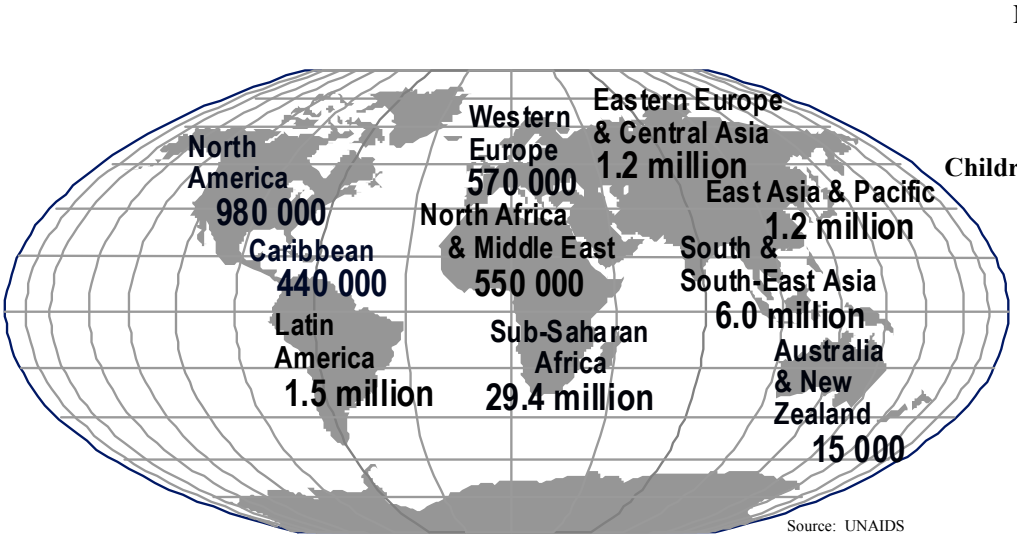
Treatment of HIV-infected adolescents is complicated by unique challenges and management demands. Particularly needed are trials to study newer drug schedules that simplify regimens, evaluation of programs to promote antiretroviral adherence in youth, and clinical trials to evaluate therapies that may exploit the immunologic resilience of recently infected youth. Also important is the development of interventions for prevention of HIV infection in youth, including HIV vaccines.

On a global basis, the HIV epidemic continues to have dramatic effect on child and maternal health. The success in reducing perinatal transmission in developed countries provides a stark contrast to the continuing perinatal HIV epidemic in developing countries, where intervention strategies that are affordable, implementable, and effective in breastfeeding women are not available. The World Health Organization (WHO) estimates that 3.2 million children are currently living with HIV infection, more than 2,000 children are newly infected every day through perinatal HIV transmission, and more than 90 percent reside in developing countries (see Figure A).

Since 1999, several shorter, less complex, and less expensive antiretroviral regimens have been shown to decrease perinatal transmission; although the efficacy of these regimens is reduced in breastfeeding infants, studies have demonstrated persistent efficacy through age 24 months. However, many developing countries are having difficulty implementing these proven prevention regimens; barriers to implementation include inadequacies in maternal-child health care infrastructure, lack of antenatal HIV counseling and testing programs, and the economic reality of severely limited resources. Studies of optimal ways to implement proven effective prophylaxis regimens are of critical importance.

Additionally, transmission of HIV through breastfeeding remains a critical problem in areas of the world where safe, sustainable, and affordable replacement feeding is not possible. Research is urgently needed to better define risk factors for HIV transmission through breastfeeding, and to develop interventions that make breastfeeding safer.

FIGURE A: ADULTS AND CHILDREN ESTIMATED TO BE LIVING WITH HIV/AIDS AS OF THE END OF 2002



Number of People Living with HIV/AIDS:

Adults: 38.6 Million
Women: 19.2 Million
Children < Age 15: 3.2 Million

Total: 42.0 Million

Youth, particularly young women, are on the front lines of the HIV epidemic in developing countries. More than 12 million youth, age 15 to 24, are estimated to be living with HIV/AIDS (most without knowing they are infected), while half of all new infections occur among young people on a global basis. Biologic, social, and economic factors make young women especially vulnerable to HIV. In some of the most affected countries, adolescent girls are being infected at a rate five-to-six times higher than boys; many of these adolescents become pregnant and, therefore, are at risk for transmitting HIV to their infants.

While use of HAART and prophylaxis against opportunistic infections has significantly modified the natural history of HIV disease in resource-rich countries, these treatments are generally not available in developing countries, where an estimated 610,000 children die annually of HIV infection. While children account for only 8 percent of those currently living with HIV infection, 20 percent of AIDS deaths have been in children, a statistic that reflects the rapid progression to disease in pediatric HIV infection, particularly in developing countries. Antiretroviral drugs are becoming less costly and more available in these countries, but optimal use of such drugs, and how best to monitor use in such settings is not known. Development and evaluation of therapeutic and prophylactic regimens relevant for children and women in resource-limited, as well as in resource-rich countries is essential.

Due to HIV-related death of the mother or of both parents, HIV/AIDS has orphaned at least 14 million children under the age of 15. Studies in developing countries have demonstrated that children born to HIV-infected mothers who die are at increased risk of death themselves, even if they are uninfected. Additionally, orphans are at particular risk of HIV infection due to social

and economic factors that increase their vulnerability to exploitation and abuse. Interventions to maximize the preservation of maternal health are critical to ensuring the health of children and families.

Thus, many challenging questions related to HIV infection in infants, children, adolescents, and women remain, which require urgent attention and scientific investigation.

MAJOR PROGRAM INITIATIVES

NICHD DOMESTIC AND INTERNATIONAL PEDIATRIC AND PERINATAL HIV STUDIES NETWORK

Background and History

PAMAB has funded the multicenter NICHD Pediatric and Perinatal HIV Studies Network and a coordinating center for the Network since 1987. Initially, funding was for the conduct of a single clinical trial to evaluate the use of intravenous immunoglobulin (IVIG) prophylaxis for bacterial infections in HIV-infected children. The Network enrolled 376 children into this trial, which subsequently demonstrated the efficacy of IVIG for this purpose. In 1989-90, the NICHD Network began to collaborate with the PACTG, which is funded by the NIAID, in conducting clinical trials, an effort that has successfully continued to the present.

The NICHD Pediatric and Perinatal HIV Studies Network Coordinating Center contract was recompeted in 1992, 1997, and 2002; under the direction of PAMAB, the Coordinating Center subcontracts with clinical sites for the conduct of studies. As the demographics of pediatric and maternal HIV infection have changed over time, the NICHD Network has expanded and modified the number and type of clinical trials sites that form the Network, as well as the types of studies being done within the Network.

In 1991, PAMAB expanded the clinical trials sites to include a specialized obstetric component for performing perinatal trials (e.g., PACTG 076), and to add an adolescent specialty component. In 1996, the Network underwent a competitive solicitation for new sites, with an emphasis on sites with large pediatric/maternal populations without access to clinical trials by other mechanisms, particularly sites in the southern United States, in which a documented expansion of the HIV epidemic among women existed. In addition, because of increased emphasis on including pathogenesis-based research questions into the conduct of clinical trials, the Network added capabilities for the performance of specialized laboratory testing in the context of clinical trials activities. The domestic Network sites were last recompeted in 2002.

In recognition of the global nature of the pediatric and maternal HIV epidemic, PAMAB began an international expansion of the Network in Latin America and the Caribbean in 1998, with the selection of two sites in Brazil, and one site in the Bahamas for the conduct of perinatal trial PACTG 316. This study evaluated whether intrapartum/newborn single-dose nevirapine further reduced transmission in women receiving standard antiretroviral prophylaxis. During 2000,

international trials were further expanded to include three additional sites in Brazil, to conduct a second study of the effect of enhanced formula on growth in HIV-infected infants. Currently, these six international sites are also participating in additional PACTG protocols. Based on experience with these clinical trials sites, PAMAB identified a need for further training and development to increase Latin American and Caribbean capacity for the conduct of clinical trials. During 2000, PAMAB began the NICHD International Site Development Initiative (NISDI) to address this need.

In addition to Network collaboration with the PACTG for conducting clinical trials, other international studies funded solely by the NICHD have been conducted through the NICHD Network Coordinating Center contract. In 1999, the NICHD Coordinating Center funded an international, collaborative, individual-patient meta-analysis involving 15 domestic and international perinatal studies; PAMAB staff led the study to address the relationship between mode of delivery and perinatal HIV transmission (see the Research Advances section of this report for more information). In 2000, PAMAB initiated an international meta-analysis of nine African perinatal clinical trials to determine the extent, timing, and risk factors for breast milk HIV transmission, and the effect of breastfeeding on maternal mortality; this effort used the international collaborative model of combining individual patient data from multiple studies, to form a large dataset with increased power to detect associations.

Also initiated in 2000, with one-time funding from the Office of AIDS Research (OAR), PAMAB and the NICHD Network Coordinating Center developed an international collaboration with investigators in India to conduct an observational perinatal antiretroviral prophylaxis prevention study in a rural health setting in Tamil Nadu, India. In 2001, PAMAB, with initial one-time funding from OAR, initiated the development of a clinical trial in Brazil to evaluate three post-exposure antiretroviral infant prophylaxis regimens to prevent transmission when the mother had not received antenatal antiretroviral therapy. A more detailed description of individual international activities follows in the NICHD Network International Studies section.

Goals and Components

In response to changes in HIV epidemiology in the United States, evolution of critical research questions over time, and the need for increased attention to development of research collaborations with resource-limited countries for HIV prevention and treatment, PAMAB diversified the activities of the NICHD Network Coordinating Center to encompass domestic and international research issues and infrastructure development, as well as the conduct of clinical trials by domestic and international NICHD Pediatric and Perinatal HIV Studies Network clinical sites. While the majority of clinical trials are conducted in collaboration with the PACTG, certain clinical trials of special relevance to the NICHD mission are conducted solely within the NICHD Network.

The primary goals of the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network include:

- Evaluating interventions to further reduce mother-to-child HIV transmission, particularly for women who are identified as HIV-infected very late in pregnancy, or at labor, and, therefore, have not received antiretroviral therapy;

- Evaluating the pharmacokinetics and safety of antiretroviral drugs in pregnant, infected women and their neonates, including metabolic and short- and long-term effects of exposure on the women and their infants;
- Identifying optimal strategies for timing therapy initiation in antiretroviral-naïve infants, children, and adolescents; determining when to change therapy in those who are antiretroviral-experienced; and finding optimal treatments for those failing therapy;
- Identifying therapies that improve the clinical status, quality of life, and survival of HIV-infected infants, children, and adolescents at all stages of disease, from early asymptomatic infection to end-stage AIDS, including antiretroviral drugs, therapies aimed at immune reconstitution, and use of therapeutic HIV vaccines;
- Identifying therapies or prophylactic regimens that prevent or mitigate the development of serious sequelae of pediatric and adolescent HIV infection, including opportunistic infections, growth abnormalities, neurologic/neurodevelopmental impairments, and other complications;
- Evaluating the long-term impact of antiretroviral therapy on HIV-infected infants, children, and adolescents, including morbidity and survival, with a particular emphasis on metabolic toxicities;
- Identifying and evaluating gender-specific manifestations of HIV and identifying therapies to treat women-specific manifestations of HIV in infected, non-pregnant women;
- Evaluating the pathogenesis of HIV disease in children and women, and that of perinatal transmission in the context of clinical trials;
- Utilizing clinical trials databases maximally, both within the PACTG and from non-PACTG studies, in cross-cutting epidemiologic investigations that focus on significant questions relevant to developing and conducting pediatric/perinatal HIV trials; and
- Assisting in training and infrastructure development at international sites in resource-limited countries to allow future participation in pediatric and perinatal clinical trials conducted within the NICHD Network.

The following provides more detail on individual activities conducted through the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network and its Coordinating Center.

Collaboration with the PACTG

The NICHD Network consists of domestic and international clinical sites that enroll study subjects in PACTG trials related to preventing and treating HIV infection and its complications in neonates, infants, children, adolescents, and pregnant women. Domestically, the Network consists of 21 centers, located in 19 cities, in 11 states/territories (including Puerto Rico); there are six international clinical trials sites: five centers in different areas of Brazil, and one in the Bahamas. The current Network trials sites are listed in Appendix D. The NICHD Network sites currently enroll approximately 1,000 subjects a year into various PACTG studies; specifically, 1,408 subjects from NICHD Network sites were in active study follow-up by July 2002 (some children may be enrolled in more than one protocol).

In addition, PAMAB staff work with staff from the NIAID Division of AIDS (DAIDS), in conjunction with NICHD- and NIAID-funded investigators, to comprise the PACTG Executive Committee. This Committee sets the scientific agenda for therapeutic research on HIV-infected

children and pregnant women in the United States. Additionally, the NICHD has developed special collaborations with other NIH Institutes, such as the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Mental Health (NIMH), as well as with other agencies, such as the CDC and the Health Resources and Services Agency (HRSA). For example, in collaboration with the NHLBI and NIAID, the NICHD developed a clinical trial to evaluate the efficacy of hyperimmune HIV immunoglobulin (HIVIG) for preventing perinatal HIV transmission. The NICHD Network Coordinating Center was the data center for the trial, which was conducted within the PACTG at both NIAID- and NICHD-funded sites. The Network plans to collaborate with the NICHD-funded ATN to conduct adolescent-specific clinical trials.

PAMAB also supports laboratory-based, pathogenesis-oriented research in the context of PACTG clinical trials. For example, PAMAB funded a central laboratory for the HIVIG protocol, to ensure that it had the capabilities to conduct specialized laboratory assays for the initial pharmacokinetic evaluations, HIV RNA assays, and antiretroviral drug resistance assays needed for the study. PAMAB also provides support to NICHD Network site investigators who have relevant laboratory expertise for the conduct of specialized pathogenesis-based studies in the context of PACTG protocols. For example, investigators from the NICHD Network site in Denver receive funding as a PACTG immunology core laboratory, to provide sophisticated immunology laboratory testing in certain PACTG protocols at both NICHD and NIAID sites.

Collaboration with the Adult AIDS Clinical Trials Group (AACTG)

For more than 10 years, PAMAB has collaborated with women's health investigators in the AACTG to support enrollment of women identified at NICHD Network clinical trials sites into AACTG protocols that are designed to answer questions related to gender-specific manifestations of HIV infection in women. NICHD Network sites have helped enroll nearly one-fourth of the women cumulatively enrolled in AACTG studies on topics such as optimal management of cervical dysplasia, interactions of antiretroviral therapies with contraceptive hormones, and metabolic complications of antiretroviral therapy during pregnancy.

PAMAB staff are also active participants in the AACTG Women's Health Committee. Current collaborations in this area include a study of the interaction of selected antiretroviral agents with the injectable contraceptive, depot medroxyprogesterone; a study of the effects of HAART initiation on genital detection of human papillomavirus (HPV) and dysplasia; an evaluation of rates of pregnancy and metabolic complications among women on protease inhibitor-containing antiretroviral regimens compared to regimens without protease inhibitors; and an evaluation of factors associated with rebound of HIV RNA levels after delivery.

NICHD Network International Studies

As the number of new, perinatally infected children decreases in the United States, the capacity to collaborate with international sites in other developed and mid-developed countries is critical to enabling the conduct of trials to evaluate the effectiveness of therapeutic and prophylactic modalities in children. Additionally, it is particularly important for the Branch to evaluate therapies that are relevant to resource-limited countries, where the bulk of pediatric HIV infection occurs, and to support infrastructure development in such countries. In addition to the PAMAB-funded international sites that collaborate in PACTG trials described above, PAMAB

also funds clinical trials activities in Latin America and India through the NICHD Network Coordinating Center subcontract mechanism.

Latin American/Caribbean NICHD International Site Development Initiative (NISDI)
UNAIDS estimates that there are currently 65,000 children under the age of 15 living with HIV in Latin America and the Caribbean; during 2001 alone, 13,000 HIV-infected children died in these countries. Perhaps more telling, in the year 2001, fewer than 400 children were newly infected with HIV in North America, as compared with 16,000 children in Latin American and Caribbean nations. During fiscal year 2000, PAMAB began an international site development initiative in Latin America and the Caribbean, NISDI, designed to provide capacity-building and training to international sites through the conduct of two descriptive studies: one in HIV-infected pregnant women and their infants; and the other in HIV-exposed, but uninfected infants and HIV-infected infants, children, and adolescents. The goal of this initiative is to develop sites that will be able to participate in future international prevention and treatment trials in collaboration with the PACTG, the HPTN, the HIV Vaccine Trials Network (HVTN), the ATN, and other relevant networks.

The initiative provides direct training and capacity-building for sites with little prior experience in conducting clinical trials, by having these sites participate in developing protocols and informed consent documents to ensure cultural sensitivity and consistency with the site's/country's research goals, by managing data collection and entry on study forms, and by performing virologic and immunologic laboratory testing and other trial-related activities. The conduct of these studies will also provide important data about the demographic, clinical, immunologic, and virologic characteristics of HIV-infected women and children who are followed at these sites, will assist in the development of an international research agenda and clinical trials relevant to these countries, and will provide critical information on the safety of antiretroviral drugs and other therapies among infected pregnant women and children in these countries.

The perinatal protocol is a prospective study to describe the characteristics of HIV-infected pregnant women and their infants who attend participating international clinical sites, where formula and antiretroviral prophylaxis of mother-to-child transmission of HIV are available. The results will describe the use of interventions related to decreasing the risk of mother-to-child transmission, including antiretroviral prophylaxis, cesarean section before labor and membrane rupture, and avoidance of breastfeeding; receipt of maternal antiretroviral therapies; maternal adverse events during pregnancy and the postpartum period; short-term infant outcomes potentially related to *in utero* and neonatal exposure to antiretroviral medications, and to mode of delivery; and mother-to-child HIV-transmission rates. HIV-infected women will be evaluated antepartum, intrapartum, and six months postpartum; infants will be evaluated through six months of age.

The pediatric protocol is a prospective study to describe the demographic, clinical, immunologic, and virologic characteristics of HIV-exposed infants and HIV-infected children and adolescents followed at NISDI sites. Prospective data collection will include medical history, physical examination, laboratory evaluations (including hematology, flow cytometry, biochemical and HIV-specific viral assays), growth parameters, morbidity, and mortality. The study will provide

critical information on the long-term safety of *in utero* and postnatal antiretroviral drug exposure in HIV-exposed, but uninfected infants, as well as information related to the long-term outcome of HAART used by HIV-infected children.

PAMAB and the NICHD Network Coordinating Center developed and released a Request for Proposal (RFP) for Latin American/Caribbean sites in November 2000, soliciting potential investigators/sites in a systematic fashion through communication with regional and national public health and AIDS offices, professional organizations, and universities. An external review committee received and reviewed proposals in 2001; six sites (located in Mexico, Argentina, and Brazil) were selected. During 2001 and 2002, PAMAB staff, with input from international investigators, developed the study protocols; an external expert panel of pediatric HIV specialists, the NICHD Institutional Review Board (IRB), separate in-country IRBs, and national review boards (where appropriate, i.e., Brazil) reviewed and approved the protocols. In addition, six sites (five in Brazil, one in the Bahamas) from the existing NICHD Network that are already participating in PACTG trials are also taking part in these protocols. Enrollment at the sites began in autumn 2002. PAMAB plans a new competition for additional sites in Caribbean nations, should funding become available.

Clinical Trial of Post-Exposure Antiretroviral Prophylaxis of HIV-Exposed Infants in Brazil

PAMAB is providing funding and leadership for a clinical trial on the efficacy and safety of neonatal antiretroviral prophylaxis for infants born to HIV-infected women who did not receive antiretroviral therapy during pregnancy. This study includes women who were first identified as HIV-infected during labor, and, therefore, were unable to receive antepartum or intrapartum prophylaxis, a situation not uncommon in many mid-developing countries such as Brazil. In fact, even in the United States, 15 percent of HIV-infected women lack prenatal care. The study will open in early 2003, in four cities in Brazil, with expansion to domestic PACTG sites expected shortly thereafter; discussions of expanding the trial in non-breastfeeding populations in NIAID-funded PACTG sites in South Africa and Thailand are also underway.

Participants in the trial will be randomized to one of three infant therapy arms: ZDV for six weeks—the standard of care to prevent transmission in this situation in Brazil and the United States; ZDV for six weeks, plus three doses of nevirapine during the first week of life; or ZDV for six weeks, plus lamivudine and nelfinavir for two weeks. Women may receive ZDV therapy during labor if HIV infection is diagnosed in time to permit administration. Current observational data suggest that neonatal ZDV may reduce perinatal transmission by about two-thirds compared to no treatment; thus, ZDV is the control arm of the trial. The combination therapy arms were included based on the enhanced efficacy of combination therapy for treating established HIV infection, and on the hypothesis that combination therapy may also have enhanced efficacy for transmission prevention without having undue toxicity for infants. This study will have broad global applicability, providing crucial data on the optimal regimen for neonatal prophylaxis that balances efficacy, safety, and cost for women whose HIV infection is diagnosed at the time of delivery in the United States and around the world.

The Perinatal HIV Transmission Prevention Project in India

While science has achieved major successes in preventing maternal-to-child HIV transmission in resource-rich countries with a relatively low burden of HIV infection among women and children, significant challenges remain with regard to preventing transmission in countries such as India, where resources are more limited, and a greater population burden of HIV infection exists.

Approximately 20 million births occur each year in India, where HIV seroprevalence rates among pregnant women have been estimated at 1 percent to 2 percent; thus, 200,000 to 400,000 HIV-infected women deliver annually. Assuming a minimal estimate of a 25 percent transmission rate without any intervention, 50,000 to 100,000 HIV-infected infants are born each year. Implementation of efficacious interventions to prevent perinatal transmission in India has been hampered due, in large part, to the expense of and infrastructure required for such interventions. However, researchers have developed more feasible interventions, and clinical trials have shown them to be effective, including simpler, short-course ZDV, and intrapartum/neonatal single-dose nevirapine regimens.

Through supplemental, one-time funding from OAR in fiscal year 2000, the NICHD Network initiated a collaboration with investigators in southern India following consultation with the Indian Council on Medical Research, the National AIDS Control Organization, and the AIDS Society of India. The initial activity of this project was selection of a pilot site for operational research on prevention of mother-to-child HIV transmission in a rural setting in India; the site has 3,500 to 5,000 antenatal clinic attendees a year and an HIV seroprevalence in pregnant women of 3 percent. The study protocol, *A Prospective Cohort Study of the Seroprevalence of, and Interventions to Decrease the Risk of Maternal-to-Child Transmission of HIV Type 1 in Tamil Nadu, India*, was drafted in collaboration with Indian investigators.

During Stage I of the study, all pregnant women registered in the antenatal clinic will be offered the opportunity to participate in an educational session about HIV infection and transmission. Pre- and post-session assessments of knowledge, attitudes, and beliefs will be administered to a random sample of women; voluntary counseling and HIV testing will be offered. During Stage II, those women identified as HIV-infected will be offered enrollment in a prospective cohort study and offered ZDV prophylaxis for the prevention of mother-to-child HIV transmission beginning at 28 weeks gestation (or as soon as possible thereafter if late presentation for antenatal care), as well as intrapartum ZDV; in addition, the study will provide six weeks of ZDV prophylaxis to the infant. All women will also receive education and counseling about the risks and benefits of breastfeeding, the factors which may increase the risk breastfeeding transmission, and the potential advantages and disadvantages of early weaning from breast milk. Researchers will perform follow-up of the mothers and children to determine rates of mother-to-child HIV transmission, according to the history of antiretroviral prophylaxis received and the child's feeding modality, and to assess 12-month morbidity and mortality.

The protocol, already approved by an independent scientific review committee, the Joint Working Group of the Indo-U.S. Maternal and Child Health and Human Development Research Program, and IRBs in India and the United States, is now undergoing final review by Indian government agencies in Delhi. Training for this protocol is likely to occur in the first quarter of 2003, with enrollment beginning shortly thereafter. Researches anticipate that approximately 105

to 150 HIV-infected women will be identified over the course of the first year of the pilot project. Following an evaluation of the pilot program, researchers will consider extending the pilot project activities to other rural settings within India, pending additional funding.

International Meta-Analysis Projects: The International Perinatal HIV Group

Early studies of the relationship between mode of delivery and vertical transmission of HIV had conflicting results; some suggested a lower risk of transmission with cesarean section, but others did not. A collaborative effort was initiated to determine what association, if any, existed between mode of delivery and perinatal HIV transmission. PAMAB staff led this international collaborative effort, which resulted in meta-analyses of individual patient data, not only to address the question of mode of delivery and transmission, but also to assess the relationship between duration of ruptured membranes and transmission. Study investigators pooled individual patient data from 15 prospective cohort studies in North America and Europe to assemble a study population sufficiently large to achieve adequate statistical power for the planned analyses. Investigators then applied uniform definitions of modes of delivery across all studies and conducted multivariate analyses that incorporated important factors related to perinatal transmission of HIV. Results of the study are presented in the Research Advances section of this report.

International Meta-Analysis Projects: The Breastfeeding and International HIV Transmission Study (BHITS) Group

Although research has conclusively demonstrated that HIV can be transmitted through breastfeeding, an improved understanding of the risk and timing of postnatal transmission through breastfeeding is needed to develop appropriate strategies for infant-feeding policies in regions of the world where complete avoidance of breastfeeding is generally not feasible. To develop this understanding, PAMAB initiated an international collaborative effort to further characterize HIV transmission through breastfeeding. Using the International Perinatal HIV Group (above) as a model, researchers pooled individual patient data from 3,442 HIV-infected women and their children who participated in nine randomized clinical trials conducted in sub-Saharan Africa, to assemble a study population sufficiently large to achieve adequate statistical power for the planned analyses. Eligible trials had to be completed, or have completed enrollment, be conducted in a population where breastfeeding was common, include regular assessment of infant-feeding modality, and have laboratory follow-up of at least two scheduled tests during the first three months of life; if follow-up continued after age three months, two additional tests between three and 12 months of life were needed. The analysis goals were to estimate the contribution of late, postnatal HIV transmission through breastfeeding to overall perinatal infection, and to clarify the timing and identify determinants of late postnatal transmission. For the purpose of the study, early transmission was defined as a diagnosis of HIV infection before four weeks of age. A child who had negative HIV diagnostic test results at, or after, four weeks of age, followed by positive test results, was classified as a late postnatal transmission case.

Conflicting results have been reported regarding maternal mortality in HIV-infected breastfeeding women in Africa; one study suggested an increased risk of mortality compared to formula-feeding women, while another showed no differences in maternal mortality by infant-feeding modality. The BHITS database represents a unique resource for further exploration of this important research topic. The goals of the BHITS analyses include providing a more reliable

estimate of the mortality risk and timing of mortality in relation to duration of breastfeeding among HIV-infected women who breastfeed over a 12- to 18-month period after delivery, and identifying factors associated with mortality in these women.

Consultation to Explore a Research Agenda to Improve the Care and Management of Mothers and Children Affected by HIV in Africa

On March 25 to 29, 2001, the NICHD and PAMAB staff led a consultation of African researchers and care providers, convened in Gaborone, Botswana, using special funding provided by OAR, to discuss and identify research needs and opportunities that would help improve the care and management of women, especially mothers, and children affected by HIV in Africa. The meeting, which was co-chaired by Yvonne Maddox, Ph.D., deputy director of NICHD, and Ruth Nduati, a pediatric HIV expert from Kenya, involved approximately 140 biomedical and social science researchers, a variety of health care providers, including traditional practitioners, doctors, nurses, midwives, pharmacists, community health workers, and others, representatives of African non-governmental and faith-based organizations, and research funding agencies. Two-thirds of the participants were African, from 12 Anglophone and Francophone countries. The consultation included 28 plenary presentations and two scientific panels. The sessions described the African context and "on-the-ground" realities that must inform all African care programs and research endeavors; reviewed the state-of-the-art in HIV/AIDS and opportunistic infection diagnosis and treatment research; discussed the role of nutrition in HIV care and management; and outlined issues of special importance to mother-infant pairs, such as safe breastfeeding. Working groups met to identify specific research questions and issues that must be addressed within the African context. A final report of the meeting and the research issues discussed was published (this report was previously provided to the NACHHD Council), as the *Report of the Consultation to Explore a Research Agenda to Improve the Care and Management of Mothers and Children Affected by HIV in Africa*, to assist the NICHD and other agencies in developing new funding initiatives related to HIV infection in women and children in Africa. The recent NICHD Request for Application, *Partnerships for HIV/AIDS Research in African Populations*, was one outcome of this meeting.

ADOLESCENT MEDICINE HIV/AIDS RESEARCH NETWORK (AMHARN)

AMHARN, funded between 1994 to 2001, was a cooperative agreement that supported a network of three functional components: a basic science group, responsible for defining the scientific agenda; interacting with a clinical science group charged with its implementation; both supported by a data and operations center. AMHARN had 15 clinical sites, in 13 cities in the United States. The Network was co-funded by PAMAB, the National Institute on Drug Abuse (NIDA), NIAID, and NIMH, but also had HRSA Title IV co-funding in its first three years, to provide infrastructure at clinical sites. Although the mission of the network was to conduct biomedical research, its scope expanded to include substantial outreach in the surrounding communities, an effort supported by HRSA funding.

The initial 12 AMHARN sites each received limited Ryan White Title IV funding through their NICHD grant awards, with which they were to design innovative ways of identifying youth and linking these youth to care. By leveraging this limited funding with *pro bono* contributions from

Madison Avenue advertising firms and with the music industry's LIFEBeat™, a program designed to reach young people with messages of HIV prevention and awareness, the AMHARN site at Montefiore Hospital conceived Project ACCESS (*Adolescents Connected to Care, Evaluation, and Special Services*). The campaign consisted of age-targeted social marketing aimed at promoting HIV counseling and testing among young people. After securing funding from the Congressional Black Caucus Emergency HIV Fund, the network selected sites in six cities on the basis of competitive applications to conduct Project ACCESS in 1999, and 2000. Through this campaign, significant synergy was fostered among youth-serving agencies in cities. Another initiative, jointly funded PAMAB and HRSA, Project TREAT (*Therapeutic Regimens Enhancing Adherence in Teens*) was a clinical program to support youth in their treatment decisions and adherence to therapy.

Although AMHARN originally planned to enroll 240 HIV-infected, and 120 uninfected adolescents between ages 12 and 19, it ultimately enrolled 325 HIV-infected, and 171 uninfected youth, with annual retention rates in excess of 85 percent. The initial study was predominantly biomedical with project objectives of examining HIV manifestations and disease progression, interaction between HIV and growth/sexual maturation, and HIV effect on co-morbidities, primarily HPV. An equally important objective was establishing normative immunologic data in adolescents as a basis for future therapeutic interventions. In addition to these primary objectives, a nutrition substudy was funded through an investigator-initiated R01 grant, while a vaccine substudy of human leukocyte antigen (HLA) typing and epitope mapping to guide vaccine design was developed in collaboration with the DAIDS. The vaccine study collected immunogenetic data from the racial and ethnic minority population enrolled in the observational study component of AMHARN, Reaching for Excellence in Adolescent Care and Health (REACH), to predict immune responses and develop assays at NIAID; nearly 100 youth from REACH participated in this vaccine study. Thus, the first in-road into basic HIV vaccine research with the American adolescent population was accomplished through AMHARN. Subject accrual for REACH ended in November 1999, and the study closed in November 2000; funding of the basic science group and the data and operations center continued through November 2001, to finish primary analyses.

Researchers from the REACH component of AMHARN have published 49 abstracts and 35 scientific papers, with an additional five papers accepted for publication, seven manuscripts in review, and at least five more papers in process. An external scientific advisory panel reviewed the scientific agenda of AMHARN in 1995, and its progress in achieving its goals in 1997. The advisory panel recommended to the NICHD director that data from AMHARN justified the development of a network that would conduct interventions in these adolescent populations, rather than continuing as a study that was purely observational in nature, which provided an impetus for the establishment of the ATN (see below).

ADOLESCENT MEDICINE TRIALS NETWORK (ATN) FOR HIV/AIDS INTERVENTIONS

The ATN was created following the recommendation of the AMHARN external scientific advisory panel that there existed a need for interventional studies in adolescents. The ATN is a national, multicenter research network, started by PAMAB in 2001, to conduct both independent

and collaborative research, with co-funding from the NIDA, NIMH, and the National Institute on Alcohol Abuse and Alcoholism, through a cooperative agreement mechanism.

The primary mission of the ATN is to conduct research, both independently and in collaboration, with existing research networks such as the HPTN, HVTN, the PACTG and AACTG, the Community Programs for Clinical Research on AIDS, and others, to explore promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV at-risk adolescents, age 12 through 24. The ATN, PACTG, and HVTN collaboration has successfully yielded a Phase I/II template for HIV vaccine trials in uninfected, at-risk adolescents that will be used once an appropriate HIV vaccine becomes available for evaluation.

ATN activities encompass the full spectrum of research needs for youth: from primary prevention, including HIV preventive vaccine trials, when available, for HIV at-risk youth in the community, to clinical management of HIV-infected youth, including novel regimens, drug adherence, and risk reduction. The ATN includes a leadership group that is responsible for defining and developing the research agenda; a data and operations center; and 15 clinical sites across the United States and Puerto Rico (see Appendix E for listing of clinical sites).

Network-Wide Needs Assessment for the ATN

In its first year of funding, the ATN undertook two efforts: (1) a community-based needs assessment of HIV-uninfected, but at-risk youth through an audio computer-assisted, self-interviewing (ACASI) strategy, in which 2,500 surveys were obtained; and (2) a similar ACASI plan, with a medical chart abstraction for the HIV-infected clinic population, that can be used as a managerial database in assessing study feasibility within the Network as studies are proposed.

Therapeutic Agenda of the ATN

The therapeutic agenda of the ATN builds particularly on the immunology findings of the REACH component of AMHARN. It includes the following studies:

- ATN 008 is a structured, treatment-interruption study that assesses "auto-vaccination" by allowing controlled HIV replication through closely observed treatment interruptions in adolescents who have successful viral suppression on HAART.
- ATN 015 is a short-cycle therapy study that is assessing an alternate approach to maintenance antiretroviral therapy in adolescents following viral suppression on HAART, comparing a "four days on, three days off" cycle to a conventional seven-day per week regimen of HAART. (Both ATN 015 and ATN 008 were reviewed by a PAMAB-established Data and Safety Monitoring Board [DSMB] and will begin enrollment in January 2003.)
- ATN 021 will pursue the pathogenesis of metabolic disorders, which was a major factor in deaths that occurred in HIV-infected adolescents enrolled in REACH.
- ATN 022 represents an external collaboration with the Institute of Human Virology at the University of Maryland, to develop the detuned HIV antibody assay for the oral testing product, Orasure®, as a method for determining recent HIV infection.
- ATN 026 will continue to pursue the vaccine-based work initiated in REACH and will evaluate HIV-specific $CD8^+$ cell responses and escape mutations as explanations for observed HLA class I allele-associated differences in HIV disease progression.

- The ATN is collaborating with the PACTG to bring a therapeutic vaccine for HPV into clinical trials for youth with dual HIV/HPV infection.

Behavioral Agenda of the ATN

The ATN is committed to implementing a Primary Prevention Program (called "P3") in all 15 ATN site cities. The goal of this program is to provide a "prevention safety net" for youth in the community by building a prevention-focused research infrastructure. In phase one of P3, the ATN will apply basic public-health principles of community mapping (both morbidities and resources) and coalition-building through a community mobilization model. At the time this report was printed, phase one, called *Connect to Protect*, was being implemented in five cities; the remaining 11 sites were trained by late 2002. The second phase of P3 will provide a menu of studies to research staff at the sites, and to their community partners, from which they may select interventions that best meet the youth needs identified in the *Connect to Protect* phase.

The behavioral scientific agenda set by the leadership group includes the development or adaptation, implementation, and evaluation of culturally appropriate, theory-driven, behavioral HIV- and sexually transmitted disease-preventive interventions for at-risk youth. The research has a special interest in innovative interventions that focus on families, partners, or other peers, as well as on studies that examine successful community implementation of HIV-prevention interventions, including community-based intervention to reduce the risk for starting drug use, and/or engaging in high-risk drug use behaviors, such as injection drug use or sharing needles, and sexual risk behaviors associated with drug use. Interventions that target highest-risk youth (e.g., street youth) who lack access to health care and social service systems are also envisioned. The behavior leadership group issued an invitation in fall 2002, for researchers to submit proposals for collaborative work in these areas that would help to achieve these scientific goals. The ATN is in the process of implementing ATN 009, which examines the health-seeking behaviors of young women with substance abuse problems, a project funded through an investigator-initiated R01 grant from NIDA. In addition, ATN 006 is conducting the formative research to implement a randomized, controlled trial to determine the most effective way of imparting HIV-prevention vaccine information to adolescents and their parents in the consent process. ATN 023 will produce a typology of the most prevalent barriers to drug adherence, so that efficient, multifaceted interventions can be developed.

WOMEN'S INTERAGENCY HIV STUDY (WIHS)

WIHS is the largest and longest ongoing cohort study of HIV-infected women. This multicenter study of the natural history of HIV infection in women is co-funded by the NICHD, NIAID, NIDA, the National Cancer Institute (NCI), and the National Institute of Dental and Craniofacial Research. WIHS consists of six clinical sites and a data center. PAMAB has funded the University of California WIHS clinical site since the study began in 1993.

The primary goal of WIHS is to describe the natural history of HIV infection in women, including risk factors, use of and response to therapy, and complications of HIV infection and therapy. With the development of HAART, HIV has become a treatable, chronic disease; therefore, WIHS is now describing the impact of therapy on HIV infection in women, including

the benefits to slowing disease progression and improving survival, the complications of therapy, the interactions with other chronic infections, such as hepatitis C, and the impact on concomitant conditions, such as genital neoplasia.

The initial cohort enrolled 2,059 HIV-infected and 569 HIV-negative women. Changes in the epidemic that resulted from the availability of more effective antiretroviral therapy, and from the aging of the cohort led to an expansion of WIHS in 2001, to enroll additional women, especially younger women, and women naïve to antiretroviral therapy, to better delineate complications of therapy versus those of aging. The expansion added 744 HIV-infected women and 408 HIV-negative women who had characteristics similar to the infected women. Because 85 percent of the enrollees are women of color, WIHS reflects the demographics of HIV infection in the United States. WIHS includes a similar control group of HIV-uninfected women to allow differentiation of complications of HIV infection and its therapy, from prevalent conditions related to poverty and aging. The WIHS investigators have authored approximately 155 peer-review publications since the study began.

WOMEN AND INFANTS TRANSMISSION STUDY (WITS)

PAMAB co-sponsors WITS, the longest continuously enrolling, prospective cohort study of HIV-infected pregnant women and their children. The study was initiated in 1988, and, through a cooperative agreement co-funded by the NICHD, NIAID and NIDA, is currently in its fourth funding cycle. The main objectives of WITS are to: identify and characterize factors that influence maternal-infant transmission of HIV; develop and evaluate methods for early diagnosis of HIV in perinatally exposed infants; and identify and characterize factors that influence HIV disease progression in HIV-infected pregnant and postpartum women and children.

As of June 2002, the six clinical sites in the United States and Puerto Rico had enrolled 2,872 HIV-infected pregnant women, and 2,396 infants born to them. In addition to collecting clinical and laboratory information on participants at regular intervals, WITS maintains a valuable repository of biological samples for current and future research. Specific aims of the current WITS cycle focus on understanding the pathogenesis and course of pediatric HIV disease in an era of antiretroviral treatment; monitoring the long-term effects of fetal and neonatal exposure to antiretroviral agents in uninfected children; describing the course of maternal HIV disease in an era of antiretroviral treatment; identifying and characterizing factors that influence the development of viral drug resistance; identifying and characterizing factors that influence adherence to medication regimens; and understanding the pathogenesis and natural history of hepatitis C virus co-infection in HIV disease. As of July 2002, WITS investigators had authored 110 primary or related publications.

HIV PREVENTION TRIALS NETWORK (HPTN)

The HPTN is an international prevention-trials collaborative group funded by NIAID, with co-funding by the NICHD, NIMH, NIDA, and the Fogarty International Center (FIC). Specifically, the NICHD co-funds HPTN studies that evaluate prevention of perinatal HIV transmission, the

safety and efficacy of microbicides in preventing sexual transmission of HIV, and behavioral interventions to reduce sexual transmission of HIV. PAMAB staff are involved in the perinatal prevention studies, while staff from several other NICHD branches are also involved in the HTPN efforts, including staff from the Contraception and Reproductive Health Branch, who are active in HPTN studies of microbicides, and staff from the Demographic and Behavioral Science Branch, who are involved in HPTN behavioral studies. PAMAB staff are medical officers on a number of perinatal HPTN protocols. These protocols are described below.

HIVNET 025: This study assessed the safety and tolerability of different concentrations of chlorhexidine (0.25 percent, 1 percent, and 2 percent) used for peripartum maternal and infant washes, to identify the highest tolerated concentration of chlorhexidine. Previous studies had shown that 0.25 percent chlorhexidine washes did not reduce intrapartum transmission, but it was hypothesized that higher concentrations might be more effective in reducing HIV in the birth canal. Women underwent cervicovaginal wash with the chlorhexidine solution at the time of each vaginal examination during labor, while babies went through additional thorough washing with the chlorhexidine solution immediately after delivery. Although perinatal maternal and infant washing with 0.25 percent and 1 percent chlorhexidine were well tolerated, washes with the 2 percent chlorhexidine solution had a high rate of maternal intolerance.

HIVNET 024: The purpose of this ongoing, double-blind, placebo-controlled Phase III trial is to determine whether antibiotic treatment administered twice during pregnancy will reduce perinatal HIV transmission. It is hypothesized that reducing chronic and acute chorioamnionitis, which was shown in several studies to be associated with increased risk of perinatal HIV transmission, through antibiotic treatment might provide an inexpensive method for further reducing transmission in resource-limited settings. The study, which is being conducted in Zambia and Tanzania, will enroll approximately 3,000 HIV-infected pregnant women at 20- to 24-weeks' gestation, and will follow the women and their infants until 12 months postpartum. In addition, to avoid stigmatization, and to investigate the impact of antibiotics on HIV-uninfected women, the study will enroll an additional 600 HIV-uninfected women. At 20 to 24 weeks of gestational age, women who are randomized to receive antibiotics will get metronidazole and erythromycin, orally, for seven days; at the onset of labor, these women will get oral metronidazole and ampicillin, every four hours until delivery. All HIV-infected women and their neonates will also receive the proven-effective, single-dose intrapartum/newborn nevirapine regimen for prevention of intrapartum transmission.

HIVNET 046: This randomized, double-blind Phase III trial will begin in early 2003, in Zimbabwe, South Africa, Tanzania, and Uganda, to assess whether breastfeeding, HIV-exposed infants who receive antiretroviral prophylaxis for the first six months of life have a lower incidence of postnatal breast milk HIV transmission. The study will evaluate the efficacy and safety of daily nevirapine provided for six months, or through cessation of breastfeeding, whichever is earliest, as compared to placebo, for the prevention of mother-to-child HIV transmission in breastfeeding infants of HIV-infected women. The study will enroll approximately 1,500 HIV-infected women and their breastfeeding infants.

HPTN 054: The purpose of this two-arm, cluster-randomized trial, currently in the final stages of development, is to determine whether a strategy of "combined access" to single-dose

nevirapine prophylaxis, where pregnant women who do not wish to have HIV testing performed can access nevirapine, as well as women who have known HIV infection, results in superior nevirapine coverage than that achieved by targeted access alone, where only women identified as HIV infected can access nevirapine. The study will also examine the safety of the two approaches. The study population will include all pregnant women who attend antenatal care services in designated clinics in areas of Zambia with high HIV prevalence. Designated antenatal clinics will be assigned to offer either targeted, or combined access to nevirapine. Study investigators anticipate that eight clinical sites will each enroll 300 women, 25 percent of whom will likely be HIV infected.

CDC/NICHD Collaboration on Interventions and Epidemiologic Studies to Reduce Mother-to-Child HIV Transmission

In 2002, PAMAB entered into a unique collaboration with the CDC, by co-funding a cooperative agreement to support two clinical trials that will assess interventions to reduce breast milk HIV transmission and improve infant survival in resource-limited countries with high HIV seroprevalence. Within the context of these trials, nested research studies will assess the mechanisms of transmission during lactation, and/or issues related to the effectiveness of these interventions, including factors that affect mode of feeding or weaning decisions, toxicity, and survival among HIV-infected women and their children, and simplified tools for monitoring drug toxicity in community-based health care facilities in resource-limited settings. Following an RFP solicitation and an external expert panel review of submitted applications, two clinical trials were selected for support. A breast milk transmission prevention trial in Kenya will evaluate the safety and efficacy of HAART given during lactation to HIV-infected women who do not require therapy for their own health, as compared to women who receive the standard intrapartum/newborn single-dose nevirapine prophylaxis of transmission. This trial will be conducted as part of a multi-site, collaborative trial with the WHO. The other clinical trial, conducted in Malawi, will compare the safety and efficacy of several different regimens of infant antiretroviral prophylaxis during the breastfeeding period for prevention of breast milk HIV transmission.

International Clinical, Operational, and Health Services Research Training Award for AIDS and Tuberculosis (ICHORTA-AIDS/TB)

The FIC ICOHRTA-AIDS/TB program provides extended support for training to foster collaborative, multidisciplinary research in resource-limited country sites where AIDS, TB, or both are significant problems. Under this program, PAMAB supports a grant from investigators at the University of Botswana, where PAMAB is also supporting a large R01 clinical trial on preventing breast milk HIV transmission.

GRANTS PORTFOLIO

PAMAB supports a growing portfolio of grants with an increasingly international focus, including animal models, for studying both perinatal HIV transmission and the effects of HIV-related therapies on development; clinical trials in women and children; and career development and training awards. A brief description of selected grants within the PAMA portfolio follows.

Animal Model Grants

PAMAB supports a number of grants that use animal models to understand various aspects of HIV infection and HIV-related therapies. Using the rat model, one investigator is studying the behavioral effects of *in utero* exposure to antiretroviral drugs in newborn rats, which are then followed to adulthood to determine whether any effects persist beyond the newborn period. A second study that uses the rat model is investigating the potential mutagenic effect of *in utero* exposure to various antiretroviral therapies. In collaboration with WITS, the latter investigator will also examine specimens from HIV-infected women and infants enrolled in WITS, to assess the mutagenic effects of antiretroviral therapies.

Two simian models, using the macaque, are also supported by PAMAB grants. The first follows normal immune development in uninfected newborn macaques, which are then followed to adulthood, and then contrasts that development to immune development in macaques postnatally infected with simian immunodeficiency virus (SIV), using both pathogenic and nonpathogenic strains of SIV. The second grant will attempt to establish a model for perinatal transmission of SIV in the macaque, to investigate potential interventions in the perinatal period. This research has a focus on administering large doses of HIV-specific neutralizing antibodies in the peripartum and early neonatal periods to prevent SIV transmission.

Grants for Clinical Trials on the Prevention of Perinatal HIV Transmission

In addition to the clinical trials carried out under the NICHD Domestic and International Pediatric and Perinatal HIV Clinical Studies Network contract, and the HPTN and CDC/NICHD cooperative agreements, PAMAB also supports a number of international clinical trials through the R01 mechanism to assess the prevention of mother-to-child HIV transmission, including transmission that occurs through breastfeeding. This research is conducted in international settings and deals with the unique questions posed by the populations in those areas.

Several PAMAB-funded clinical trials are complete and their results published, including two trials conducted in Tanzania and Malawi, investigating the use of micronutrients to reduce mother-to-child HIV transmission, a study comparing breastfeeding to formula feeding by HIV-infected women in Kenya, and a study assessing the relative contributions of the antenatal and postnatal components of a short-course ZDV regimen for preventing the transmission of HIV in non-breastfeeding women in Thailand.

Investigators from the Kenya breastfeeding study (now complete) recently received a new grant to investigate the effect of cytotoxic T-lymphocytes on the risk of HIV transmission in breastfeeding, HIV-exposed infants. Additionally, researchers from the Thailand short-course ZDV study received a new grant that will allow them to compare the following therapies to determine whether nevirapine offers additional protection from transmission: a simplified

antiretroviral prophylaxis approach that uses ZDV in both mother and infant alone, the regimen shown effective in their first study; or the previous regimen combined with single-dose nevirapine given both intrapartum to the mother, and to the infant at age 48 hours; or the combination regimen with nevirapine given just intrapartum to the mother alone.

Two new large grants that are just starting to enroll participants are exploring additional issues of HIV transmission via breastfeeding. The first, in Botswana, is using a factorial design to investigate the combined effects of single versus combination antiretroviral prophylaxis (short-course ZDV alone versus ZDV combined with single-dose nevirapine), and antiretroviral treatment of the infant during breastfeeding versus formula feeding for preventing HIV transmission; the second study, in Zambia, is comparing the effect of abrupt versus prolonged (standard) weaning from breast milk, following exclusive breastfeeding for four-to-six months, for reducing postnatal HIV transmission.

Grants to Study HIV in Children

In addition to funding studies of HIV transmission from mother-to-child, PAMAB also supports a portfolio of R01 grants related to immune system development, susceptibility to HIV infection, and the progression of HIV-related disease in infants and children, as well as the impact of HAART in children both in the United States and in international settings.

Among the areas of study, one grant is exploring the kinetics of viral and T-cell turnover to determine whether the high viral loads seen in HIV-infected children are the result of increased viral production or decreased clearance of virus, as compared to adults. The effects of tissue penetration and intracellular metabolism of antiretroviral drugs on viral evolution and the development of resistance are also being examined.

Understanding the factors related to HIV disease progression in children is the topic of a number of PAMAB-supported grants. Studies that are carried out in the United States are often complex, laboratory-based studies of either the characteristics of the virus, or some aspect of the child's immune system, while the international studies focus on ways of monitoring disease progression that employ lower levels of technology. Studies of children in the United States include a focus on the dynamics of viral replication and T-cell turnover, with a long-term objective of determining the impact of HAART on T-cell regeneration by thymus-dependent and thymus-independent pathways. Other work is assessing the changes in biologic phenotype and genetic complexity in M-tropic viruses that emerge in children treated with HAART, and to evaluate interactions between HIV envelope glycoproteins and cellular chemokine receptors. The role of dominant $CD8^+$ T-cell clones in disease progression and response to antiretroviral therapy in children is the focus of a third grant.

PAMAB support of research in HIV-infected hemophiliac children was initiated in 1988, with funding of the Hemophilia Growth and Development Study, a cooperative agreement co-sponsored by the NICHD, NCI, NIMH, and HRSA; this study completed patient follow-up in 1998. PAMAB is providing continued support to research on HIV-infected hemophiliac children through the R01 mechanism, including research that will focus on the host factors that influence hepatitis C and HIV co-infection in this population.

As anti-HIV therapy becomes more successful in prolonging life, issues around therapy compliance have become more important; several branches at the NICHD support research in this area. PAMAB supports one grant that examines adherence to therapy in perinatally infected children who are receiving HAART. The study will examine many factors as possible indicators of adherence, include severity of the child's illness (both at entry and over time), medication history, duration of current regimen, demographic characteristics of the caregiver and the child, caregivers' HIV knowledge and health beliefs, complexity of the medication regimen, and other caregiver-related issues.

Different means for assessing disease progression in HIV-infected children in international settings are the focus of two grants funded by PAMAB. One examines the utility of beta-chemokines as both an indicator of disease progression, and a predictor of response to therapy with antiretroviral drugs, while a second grant takes a much lower-technology approach to resource-limited settings and attempts to use a combination of parameters (e.g., age, gender, growth velocity, and ethnicity) to predict antiretroviral therapy failure.

In addition, a study in Zambia focuses on evaluating clade C isolates of HIV from perinatally infected infants, to identify differences from clade B HIV in host cell tropism, genetic diversity, and sequence evolution, and to understand the implications of such differences for disease progression in children. Clade B HIV is the type usually seen in infected individuals in the United States. Work in Tanzania is also examining the role of viral recombinants of subtypes A, C, and D in increasing the risk for HIV transmission from mother-to-child. Another grant is exploring variations in development and persistence of resistance to nevirapine in Ugandan HIV subtype A and D isolates, following single-dose nevirapine prophylaxis to reduce mother-to-child HIV transmission.

Career and Training Grants

PAMAB continues to expand its career training awards with a mix of K08 (Mentored Clinical Scientist Development Award), K23 (Mentored Patient-Oriented Research Career Development Award), K24 (Mid-Career Investigator Award in Patient-Oriented Research), F31 (Minority Pre-Doctoral Fellowship Program), and F32 (Individual National Research Service Award) grants. The majority of these career awards support work conducted in international settings that is linked to existing NICHD- or NIAID-funded grants. A brief description of selected grants follows.

One K08 grant is attempting to further elucidate the cellular and molecular bases of the interrelationship of genital ulcer disease and HIV transmission in women. The K23 grants include one evaluating the relationship of diarrheal and respiratory diseases to breastfeeding versus formula feeding in HIV-exposed infants in Botswana. Another K23 grant is investigating infant immune responses and maternal-to-child HIV transmission via breastfeeding in Kenya. An investigator funded by a K24 grant is characterizing the HIV-specific, cytotoxic T-lymphocyte response in HIV-exposed infants, while mentoring several trainees to prepare them to become independent investigators.

PAMAB also supports two F31 grants that are underway in South Africa and Thailand. The first is related to breastfeeding and HIV transmission, while the second is investigating the decision-

making process by which pregnant women decide to undergo HIV testing. PAMAB funds one F32 grantee who is studying the use of sodium dodecyl sulfate to inactivate HIV in breast milk as a possible means of making breastfeeding a safer option in resource-limited countries.

RESEARCH ADVANCES

The remainder of this report highlights some of the research advances from PAMAB-supported scientists and Branch staff that have occurred since the last Branch report in 1999. These advances are organized into four major topic areas based on populations of interest: HIV-infected pregnant women and their infants, for studies on prevention of mother-to-child HIV transmission; pediatric HIV infection; adolescents and HIV infection; and HIV infection in women.

HIV-INFECTED PREGNANT WOMEN AND THEIR INFANTS

Maternal Viral Load and Perinatal HIV Transmission

Data from PACTG 185, a clinical trial co-funded by the NICHD, NIAID, and NHLBI, combined with data from WITS elucidated the critical role of maternal viral load in perinatal transmission. Investigators from both studies published concurrent papers the *New England Journal of Medicine* in August 1999, describing their findings.

PACTG 185 was a placebo-controlled clinical trial designed to determine the effects of HIVIG compared to IVIG without HIV antibody on transmission among HIV-infected women with advanced disease who were receiving ZDV prophylaxis. At the first interim analysis, the transmission rate in the overall group was an unexpectedly low 4.8 percent, a figure that did not differ between HIVIG and IVIG groups; therefore, the trial was stopped early. Investigators used stored samples from 480 women in PACTG 185 to assess maternal HIV RNA levels during pregnancy, and to correlate these with transmission risk. While entry and delivery maternal RNA, HIV culture titer, and p24 antibody levels, maternal $CD4^+$ count at entry, and diagnosis of chorioamnionitis were associated with transmission in univariate analyses, only maternal HIV RNA level was associated with transmission in a multivariate analysis; HIV RNA levels at delivery were the most strongly associated with transmission. For every one $\log_{10}$ increase in HIV RNA level, there was a 2.4-fold increase in risk of perinatal transmission.

WITS, co-funded by the NICHD, provided similar results from its analysis of data from 552 HIV-infected pregnant women. Increasing geometric mean levels of plasma HIV RNA were associated with increased transmission; the highest rate of transmission, 63 percent, was among women whose plasma RNA levels exceeded 100,000 copies/mL, and who had not received ZDV prophylaxis, compared to no transmission observed among women with HIV RNA levels less than 1,000 copies/mL. RNA levels did not correlate with timing of transmission (*in utero* versus intrapartum).

These combined data suggested that potent antiretroviral therapy, which reduces HIV RNA levels to below quantification, might, in addition to improving the health of the woman herself, also result in further reductions in the risk of mother-to-child transmission.

Maternal Antiretroviral Therapy and Perinatal HIV Transmission

Following the analyses on the association of viral load and transmission, data from WITS were also used to examine the interrelationship between maternal viral load, antiretroviral therapy, and perinatal transmission. Investigators examined HIV RNA levels and antiretroviral treatment status data from 1,542 HIV-infected pregnant women who were followed between January 1990, and June 2000, in addition to their correlations with transmission. Transmission was 20 percent for women not receiving antiretroviral therapy; 10 percent for those receiving ZDV alone; 4 percent for those receiving dual therapy; and 1 percent for those receiving HAART. Transmission also varied by delivery HIV RNA levels, with 23 percent transmission if RNA levels were more than 30,000 copies/mL; 15 percent if levels were between 10,000 and 29,999 copies/mL; 9 percent if levels were between 3,500 and 9,999 copies/mL; 5 percent if levels were between 400-3,499 copies/mL; and 1 percent if levels were less than 400 copies/mL. The level of HIV RNA at delivery and prenatal antiretroviral therapy were independently associated with transmission. The protective effect of therapy increased with the complexity and duration of the therapy regimen, with HAART associated with the lowest rates of transmission.

While reports from studies such as WITS and PACTG 185 indicated that maternal viral load was a critical predictor of perinatal transmission, investigators did not identify a threshold below which transmission did not occur, and some studies have described cases of transmission in women who had low or undetectable viral loads. To evaluate risk factors for transmission in women who had a low viral load at or near delivery (less than 1,000 copies/mL), researchers combined data of 1,202 HIV-infected women from seven European and United States prospective studies, including several studies supported by PAMAB, for a meta-analysis. Mothers who received antiretroviral therapy (primarily ZDV alone) had a 1 percent transmission rate, compared to 10 percent for untreated mothers. In a multivariate analysis, transmission was significantly lower in women who received antiretroviral therapy, who had higher $CD4^+$ cell count, who underwent cesarean delivery, or who had infants of higher birth weight. These data demonstrated the importance of antiretroviral prophylaxis in reducing perinatal transmission, even in the face of low maternal viral load, and suggested that perinatal transmission may be almost eliminated with antiretroviral prophylaxis accompanied by suppression of maternal viremia.

These data and the results of the meta-analysis led to major changes in United States Public Health Service recommendations for prevention of perinatal transmission. Currently, HAART is recommended for antenatal treatment of women with HIV RNA levels greater than or equal to 1,000 copies/mL, while antiretroviral prophylaxis with either ZDV alone, or in combination therapy, is prescribed for women with HIV RNA levels less than 1,000 copies/mL.

Mode of Delivery and Perinatal HIV Transmission

The primary hypothesis of the International Perinatal HIV Group meta-analysis, funded by PAMAB, was that HIV-infected women who underwent cesarean section before labor and before membranes had ruptured, called elective cesarean delivery (ECS), would have a lower risk of

HIV transmission to their infants compared to women who went through other modes of delivery. The primary analysis included data from 15 international studies on 8,533 mother-child pairs. In adjusted analyses, the likelihood of vertical transmission of HIV was approximately 50 percent lower with ECS compared to other modes of delivery, and 87 percent lower among women who had ECS combined with antiretroviral therapy during the antepartum, intrapartum, and postnatal periods (mostly ZDV monotherapy), as compared with other modes of delivery and the absence of such therapy. Although antiretroviral prophylaxis was associated with lower transmission rates regardless of delivery modality, transmission rates were lower with ECS than with other modes of delivery regardless of whether or not the women received antiretroviral therapy; transmission was 10 percent with ECS without antiretroviral therapy, compared to 19 percent with other modes of delivery without antiretroviral therapy. The respective rates with antiretroviral therapy during the antepartum, intrapartum, and postnatal periods were 2 percent and 7 percent.

The results of this meta-analysis demonstrated that ECS could effectively reduce mother-to-child HIV transmission. This finding was later confirmed by a European randomized clinical trial of mode of delivery for prevention of HIV transmission. Based in large part on the results of this meta-analysis, along with the European trial, the American College of Obstetricians and Gynecologists (ACOG Committee Opinion 234, May 2000) and the United States Public Health Service recommended that ECS be discussed and recommended for all HIV-infected women who had viral loads greater than 1,000 copies/mL, regardless of whether or not they were taking antiretroviral therapy.

Duration of Ruptured Membranes and Perinatal HIV Transmission

Some studies associated a longer duration of ruptured membranes with an increased risk of HIV transmission. However, once the lower risk of transmission with ECS was established, investigators had to determine whether the duration of ruptured membranes remained a risk factor for transmission among HIV-infected women who delivered vaginally, or among those who delivered by cesarean section after the onset of labor and rupture of membranes, or among both groups. PAMAB-supported researchers used data from the International Perinatal HIV Group, including 4,721 deliveries with membrane rupture duration of 24 hours or less, to address this issue. In adjusted analyses, the risk of perinatal HIV transmission increased approximately 2 percent with each one-hour increase in duration of ruptured membranes. Among women diagnosed with AIDS, the estimated probability of transmission increased from 8 percent to 31 percent with membrane rupture duration two hours and 24 hours, respectively. The results of these analyses support the importance of membrane rupture duration as a risk factor for perinatal HIV transmission and suggest that a diagnosis of AIDS in the mother at the time of delivery could potentiate the effect of ruptured membrane duration.

Maternal Antiretroviral Therapy and Pregnancy Outcome

Some European studies have suggested higher rates of preterm delivery and low birth weight among infants born to HIV-infected women who receive combination antiretroviral therapy during pregnancy, compared to single-drug, or no therapy. Because HAART is now recommended for HIV-infected pregnant women with HIV RNA levels greater than or equal to 1,000 copies/mL, a possible association between HAART and adverse pregnancy outcome was of great concern.

A meta-analysis was conducted using data from seven trials and studies from the United States, including PACTG 185, PACTG 076, WITS, and two PAMAB-supported R01 prospective cohort studies. The analysis compared adverse pregnancy outcomes for 1,143 antiretroviral-untreated women, who delivered prior to March 1994, and 2,123 antiretroviral-treated women, with subsequent deliveries. Preterm delivery was not significantly associated with either receipt or type of antenatal antiretroviral therapy. Thus, while continued assessment of the effects of antenatal antiretroviral therapy on pregnancy outcome is important, current combination antiretroviral regimens do not appear to be associated with a significant risk of adverse outcome. Combination antiretroviral therapy offers significant benefit to maternal health by treating HIV infection, and to infant health by reducing the risk of mother-to-child transmission.

Perinatal HIV Transmission Prevention Trials

PAMAB has supported a number of important large clinical trials on prevention of perinatal transmission in the developing world through investigator-initiated R01 grants. The standard, basic antiretroviral regimen used for preventing mother-to-child transmission in the United States is based on data from the placebo-controlled, PACTG 076 clinical trial: ZDV given orally during pregnancy starting after 14 weeks' gestation, given intravenously during labor, and given to the neonate for six weeks. In 1998, a placebo-controlled clinical trial conducted in Thailand by the CDC demonstrated that a shorter ZDV regimen, given to the mother starting at 36 weeks' gestation and orally intrapartum, also reduces the risk of mother-to-child transmission, although less so than the full antenatal-intrapartum-neonatal ZDV regimen.

A PAMAB-supported study of non-breastfeeding HIV-infected pregnant women in Thailand investigated the relative contribution of maternal and infant components of antiretroviral prophylaxis. A four-arm, factorial trial design compared antiretroviral regimens with differing durations of antenatal and neonatal ZDV treatment: antenatally starting at 28 weeks' gestation, orally intrapartum, and six weeks to the neonate (long-long); antenatally starting at 28 weeks' gestation, orally intrapartum, and three days to the neonate (long-short); antenatally starting at 36 weeks' gestation, orally intrapartum, and six weeks to the neonate (short-long); and antenatally starting at 36 weeks' gestation, orally intrapartum, and three days to the neonate (short-short). At an interim analysis, the transmission rate in the short-short arm was 10 percent, a rate significantly higher than for the long-long arm, which led researchers to discontinue the short-short arm of the trial. Even though a short antepartum-intrapartum ZDV regimen similar to the short-short arm of this trial was effective in reducing transmission compared with no therapy in the CDC study, this trial demonstrated that a somewhat longer course of ZDV had greater efficacy than a shorter course of ZDV. Additionally, the final analysis demonstrated a higher rate of *in utero* transmission among women in the short antenatal arms, compared to those receiving longer antenatal therapy, which suggests that longer infant treatment cannot substitute for longer treatment of the mother.

In a study funded by NIAID in Uganda, a regimen of nevirapine that was given as a single dose to women at the onset of labor, and as a single dose to the infants at age 48 hours reduced the risk of perinatal transmission by 47 percent in women who had not received antenatal antiretroviral therapy.

In a PAMAB-supported follow-up to the four-arm Thailand ZDV study mentioned above, the same investigator is evaluating short-course ZDV prophylaxis (starting at 28 weeks in the mother, and given for one week to the infant) alone, compared to ZDV in combination with maternal/infant single-dose nevirapine, or maternal nevirapine alone. Recently, at the first interim analysis, the DSMB recommended discontinuing the ZDV-alone arm because transmission was significantly higher than in the arm that combined ZDV with maternal/infant nevirapine; enrollment is continuing into the other two arms.

In the United States and other developed countries, standard antiretroviral prophylaxis includes HAART given to women with HIV RNA levels greater than or equal to 1,000 copies/mL (or ZDV alone if the woman's HIV RNA level is less than 1,000 copies/mL), intravenous ZDV during labor, and six weeks of ZDV given to the infants. It was unclear if adding single-dose nevirapine to this longer and more-complex regimen would offer additional benefit. To address this issue, PACTG 316 enrolled 1,506 women and their infants in Europe, in NICHD- and NIAID-supported sites in the United States, as well as in the NICHD-supported international sites in Brazil and the Bahamas, to assess whether enhancing the regimen with single-dose nevirapine offered any additional benefit in reducing transmission in women who receive standard antiretroviral prophylaxis (more than 75 percent of women receiving combination therapy), compared to nevirapine placebo. The study found remarkably low transmission rates, 1.5 percent, and no difference between study arms (1.4 percent and 1.6 percent, nevirapine and placebo, respectively). Additionally, viral genetic mutations associated with nevirapine resistance were detected at six weeks postpartum in 15 percent of women who received single-dose nevirapine. Based on these data, in situations where no antiretroviral therapy is available or only short-course ZDV is available, the single-dose nevirapine regimen offers a significant reduction in perinatal transmission risk. However, in countries like the United States, where HIV-infected women receive antenatal antiretroviral therapy (in most cases, HAART) as the standard of care, the addition of single dose nevirapine showed no significant benefit and was associated with a risk of developing nevirapine resistance.

Two other PAMAB-supported R01 studies evaluated the efficacy of nutritional supplements on preventing perinatal transmission in resource-limited settings. A study in Tanzania, with a four-arm factorial design, randomized women to receive one of the following regimens during pregnancy and lactation: multivitamins (B, C, and E), excluding vitamin A; multivitamins with vitamin A (5,000 IU daily, with a additional dose of 200,000 IU at delivery); vitamin A alone; or placebo. Significant decreases in adverse pregnancy outcomes, including low birth weight, prematurity, and infant mortality were observed in those who received multivitamins; however, there was no significant effect on *in utero* or intrapartum HIV transmission with either multivitamins or vitamin A.

In a secondary subset analysis of breastfeeding transmission, vitamin A supplementation was paradoxically associated with higher rates of breast milk transmission, while multivitamins reduced overall transmission among immunologically and nutritionally compromised women. In a second study in Malawi that evaluated vitamin A supplementation alone (10,000 IU daily, with an additional dose of 200,000 IU at delivery), given only during pregnancy, investigators observed no significant effect on reducing (or increasing) transmission.

Prevention of Transmission of HIV through Breast Milk

The risk of postnatal HIV transmission through breastfeeding creates a significant dilemma for HIV-infected women in many resource-limited settings. For instance, while replacement feeding may protect the infant against HIV infection, it may also place the infant at risk of dying from diarrheal and respiratory infections. To assess the benefits and risks of breastfeeding versus formula feeding for HIV-exposed infants, a PAMAB-supported randomized trial of breastfeeding versus formula feeding was conducted with 401 HIV-infected women and their infants in Nairobi, Kenya, in an urban area where clean municipal water was available. This study demonstrated that: breastfeeding nearly doubled the risk of HIV transmission, with an infection rate at 24 months of 37 percent in breastfed infants compared to 21 percent in formula-fed infants; and the majority of transmission appeared to occur during the early breastfeeding period, with 75 percent occurring during the first six months of life, although the risk of transmission persisted throughout the breastfeeding period. The absolute risk of breast milk HIV transmission was 16 percent. In addition, the two-year mortality rates for the two arms were similar: among infants who were HIV-uninfected, the mortality rate was 8 percent among breastfed infants and 10 percent among formula-fed infants; among those who were HIV-infected, mortality was 46 percent and 40 percent, respectively. The incidence of diarrhea, pneumonia, and other illnesses during the two years of follow-up were also similar between treatment arms. However, breastfed infants had better nutritional status during the first six months of life.

The study also reported the surprising finding that mortality among HIV-infected women was higher in the breastfeeding arm than in the formula-feeding arm, with a cumulative probability of maternal death at 24 months postpartum of 11 percent in the breastfeeding group and 4 percent in the formula-feeding group. It was hypothesized that the metabolic demands of lactation, in a population that had inadequate nutritional intake, could result in substantial nutritional impairment, which could lead to maternal weight loss, wasting, and death. The results also showed an association between maternal death and subsequent infant death, regardless of the infant's HIV-infection status.

Data from the Kenya study suggest that replacement feeding benefits both the infant and the mother, in urban, resource-limited settings with access to clean water, without inducing excess infant morbidity. However, this may not be true in other resource-limited settings, particularly in rural areas where access to clean water may be more limited, and where there may be significant cultural pressures to breastfeed. Therefore, the development of strategies to reduce the risk of HIV transmission in breastfeeding women remains a critical research challenge.

Risk Factors for Breast Milk HIV Transmission

PAMAB-funded scientists have published a number of papers that describe risk factors for HIV transmission during the breastfeeding period. For instance, women seroconverting during lactation are at high risk of transmitting to their infants, likely due to the high viral load in such situations, which highlights the importance of primary prevention of HIV acquisition in breastfeeding women in resource-limited countries. Other clinical risk factors associated with increased risk of perinatal transmission include bleeding or cracked nipples, subclinical (defined as elevated sodium levels in milk) and clinical mastitis, and breast abscesses. Infant oral thrush at less than six months of age, and breastfeeding for more than 15 months are also associated

with enhanced transmission. Further, low maternal $CD4^+$ cell count, and high maternal sedimentation rate, as well as plasma and breast milk viral load (both HIV RNA copy number and cell-associated HIV DNA levels) are associated with higher risk of transmission. The BHITS meta-analysis demonstrated a relatively constant risk of late transmission (occurring at older than one month of age) throughout the breastfeeding period.

PEDIATRIC HIV INFECTION

Fundamental to the prevention and control of pediatric HIV infection are: (1) understanding its etiology, natural history, and pathogenesis; (2) developing and evaluating diagnostic methods for the condition and its complications; and (3) identifying predictors of disease progression. Such information permits targets for and timing of diagnostic evaluation and allows therapeutic interventions to be identified and optimized. It is essential for the rational development and evaluation of new agents and interventions to prevent or treat HIV infection and disease.

Published results of research conducted in cohort studies and clinical trials that have been sponsored and co-sponsored by PAMAB since 1999, provide continued contributions to scientific understanding in each of these three areas, as well as to corresponding progress in development and evaluation of new therapies.

Understanding the Natural History of Pediatric HIV Disease

Abnormalities in neurodevelopment are one of the major manifestations of pediatric HIV infection; WITS has allowed critical research on the nature, extent, timing, and frequency of adverse effects on neurodevelopment in HIV-infected children. WITS researchers documented early and marked cognitive and motor delays or declines in HIV-infected infants compared with uninfected infants, showing differences apparent by four months of age, independent of other risk factors for developmental delay. The well-characterized and relatively complete information available on the WITS cohort of HIV-infected or exposed infants and children allowed investigators to determine that neither prenatal exposure to illicit drugs, nor primary language other than English was associated with abnormal development, and to suggest that the abnormalities the research defined could be important early indicators of HIV disease progression.

Evaluating Methods for Diagnosis of Infant HIV Infection

Prompt initiation of appropriate medical management, treatment, and monitoring of HIV-infected infants depends on the early and accurate identification of the condition. Because all infants born to HIV-infected women initially have HIV antibodies, serological testing for HIV antibodies cannot be used to distinguish infected from uninfected infants during the first several months. Early identification of infected infants, therefore, relies on viral isolation or detection of viral nucleic acid. Because these techniques were only recently developed and made available, experience with performing nucleic acid testing for infant HIV diagnosis is still accumulating. Furthermore, determining the time when HIV first becomes detectable in an infant who has perinatally acquired infection provides information about the timing and mechanism of transmission from mother to fetus or infant.

In addition to a number of previous authoritative publications on the performance characteristics of different diagnostic methods and specimen types for infant HIV diagnosis, WITS investigators added to the knowledge cache regarding infant diagnosis with a July 2000, collaborative publication. Combining data from four multicenter studies, the researchers determined that, among infected infants, approximately one-third had HIV that was detectable at birth; and that the median time to viral detectability in those without HIV that was detectable at birth was approximately 15 days. They observed no association between the timing of viral detectability and whether delivery was vaginal or cesarean, nor did they note any evidence that ZDV prophylaxis delayed the diagnosis of infant infection. These results provide information useful to guide management of HIV-exposed newborns and the use of diagnostic laboratory resources.

Identifying Predictors of Pediatric HIV Disease Progression

Several PAMAB-supported studies have characterized the usefulness of selected laboratory and neurodevelopmental markers for predicting clinical disease progression in pediatric HIV infection. WITS researchers evaluated the timing of acquisition of infant HIV infection and its effects on neurodevelopmental outcomes. Comparing infected infants in whom viral isolation was positive at, or close to birth, with infected infants in whom viral isolation was negative at birth, but positive later, the investigators determined that both cognitive and motor performance was poorer and declined more rapidly among infants with early infection. Early HIV infection increased a child's risk for poor neurodevelopmental function in the first 30 months of life, a finding that may help to improve the management of infected infants through early identification of morbidity risk, which would allow better timing of preventive or therapeutic interventions.

In addition, PACTG investigators published a meta-analysis of five, large clinical trials that evaluated how changes mediated by antiretroviral treatment in HIV RNA and $CD4^+$ lymphocyte levels predicted clinical outcomes. In a study of more than 1,000 infants and children who were receiving nucleoside reverse transcriptase inhibitors, with or without non-nucleoside reverse transcriptase inhibitors, higher $CD4^+$ cell counts and lower HIV RNA levels both at baseline and after 24 weeks of treatment were significant independent predictors of survival. Among children older than one year of age, but not in younger infants, higher RNA levels predicted weight growth failure or cognitive failure. The finding of differential age effects on pediatric-specific clinical outcomes emphasizes the need for continued investigation of treatment effects in children.

While HIV RNA levels and $CD4^+$ lymphocyte counts are the standard approaches to evaluating and monitoring HIV-infected children and adults in developed countries, less technically demanding, cheaper, and more rapid tests are needed for resource-limited settings. Data from the NICHD IVIG Clinical Trial, which was conducted from 1988 to 1991, prior to approval of antiretroviral drugs for children, were used to evaluate the predictive value of a number of simpler markers of disease for disease progression and mortality, including immune complex-dissociated (ICD) p24 antigen, HIV p24 antibody, and total lymphocyte count (TLC). Researchers found that all three markers had significant correlations with disease progression and/or mortality. The ICD p24 antigen and TLC were independently predictive of mortality risk, a result similar to previous findings from the same cohort for HIV RNA levels and $CD4^+$ lymphocyte count. These findings suggest that simpler laboratory measures could be used to

identify children at high risk of disease progression or mortality, as an alternative to more expensive and technically difficult assays in resource-limited settings.

Antiretroviral Treatment and the Course and Complications of HIV Disease

Like many other chronic illnesses, pediatric HIV infection adversely affects the normal growth that is a predictable attribute of healthy infants and children. PAMAB-supported investigators demonstrated that infants with perinatally acquired HIV infection exhibit impaired weight, length, and head growth. These early growth deficits appear to persist, and in some cases, to increase in children of preschool and school age. Poor growth is reported in as many as half of HIV-infected children. Despite its clear beneficial effects on other measures of HIV disease progression, antiretroviral chemotherapy that is currently available has not demonstrated an ability to preserve or restore normal growth in HIV-infected children.

Using data from more than 900 children enrolled in PACTG 219, a long-term follow-up study of children enrolled in PACTG clinical trials, researchers evaluated the impact of protease inhibitor-containing HAART on height and weight growth in HIV-infected children. When compared with a reference group of healthy children, the mean height of HIV-infected children was at the 18th percentile, while mean weight was at the 34th percentile. Patients who received protease inhibitor treatment experienced very small, but statistically significant annual growth increments in height and weight, compared with growth in children on regimens that did not contain protease inhibitors.

Combination therapy, including protease inhibitors, is known to be effective in treating HIV-infected adults, but only limited data is available regarding the use of this treatment in children and adolescents. Using data from PACTG 219 that examined 1,028 HIV-infected children and young people, age birth to 20, who were enrolled in NICHD- and NIAID-supported clinical trials centers prior to 1996, researchers found that initiating combination therapy that includes a protease inhibitor reduced the risk of death by 67 percent, after adjustment for potentially confounding factors indicative of severity of illness. The reduction in risk was similar among all children, regardless of age, sex, CD4 percentage, educational level of parent/guardian, or race or ethnic group. This study, in combination with other studies from the PACTG, demonstrated a decreased risk of death, improved growth, better immune function, and a marked decrease in the incidence of infectious complications with use of combination therapy in HIV-infected children and adolescents, as had been observed in adults.

However, in infected adults who were treated with long-term combination therapy, metabolic complications have begun to emerge, including lactic acidosis, hyperglycemia, hyperlipidemia, lipodystrophy, and bone mineral loss, including osteonecrosis. Research has begun documenting similar complications in children. Data from PACTG 219 demonstrated an increased incidence of Legg-Calve-Perthes Disease (osteonecrosis of the hip) in HIV-infected children, compared to data from the overall pediatric population in the United States. As HIV disease is transformed from a fatal to a chronic illness in developed countries, it remains critical to continue long-term follow-up of children, to assess the long-term outcomes of such therapies.

Treatment of HIV Infection

Data from NICHD Network-PACTG collaborative therapeutic drug trials have significantly accelerated pediatric licensure for antiretroviral medications. Additionally, these trials allow researchers to gather information regarding dose optimization, age-specific pharmacokinetic variability, drug interactions, and long-term safety data, to better manage antiretroviral medications in HIV-infected children.

New Antiretroviral Chemotherapeutic Agents and Regimens in Children

PACTG 382 is a Phase I/II, open-label study that sought to determine the pharmacokinetics, safety, tolerability, and antiviral activity of efavirenz, a highly potent, non-nucleoside reverse transcriptase inhibitor, in combination with nelfinavir and one or two nucleoside analogue drugs. This study was designed for treatment-experienced children and was used for pediatric registrational purposes. Importantly, real-time pharmacokinetic measurements were used to individualize patient dosing. The study contributed essential data for pediatric licensing of efavirenz, and for both efavirenz and nelfinavir dosing recommendations, and resulted in approval of efavirenz for adults and children, simultaneously. The study continues to evaluate dosing requirements for infants using a liquid formulation.

PAMAB researchers are also studying the use of several new agents in children, while these agents are simultaneously being evaluated in HIV-infected adults. P1020 is evaluating atazanavir, a new protease inhibitor that may have utility in children for treating viruses with resistance to some of the other protease inhibitors. Children tolerate the drug well, but initial dosing based on adult data demonstrated inadequate drug levels in children; therefore, higher doses are currently under evaluation. PACTG 1005 is a Phase I/II study of T-20, a member of a new class of HIV drugs, the HIV fusion inhibitors, in children whose current antiretroviral regimen is failing. Data suggest the drug was safe, well tolerated, and associated with significant viral load decrements in this population.

PACTG 356 evaluated very early initiation of HAART in young infected infants. This study demonstrated that three- and four-drug combination therapy, used as early as two weeks of age, could potently suppress viral replication to below quantifiable levels for prolonged periods of time. The viral kinetics in young infants approximated those seen in adults, with the youngest infants having the slowest rates of HIV turnover. This study confirmed the central role of HIV replication in the pathogenesis of HIV infection in young infants. Additionally, it demonstrated that viral replication could be suppressed in some children up to four years. Interestingly, infants whose therapy started before three months of age routinely failed to develop multiple HIV-specific immune responses (e.g., antibody, cytotoxic T-lymphocyte, and lymphocyte proliferation) as opposed to infants whose therapy started when they were older than three months. This finding led investigators to plan an evaluation of administering an HIV vaccine in infants who are on HAART and have prolonged virologic suppression, to assess whether the HIV-specific immune response can be boosted and viral suppression maintained.

While the protease inhibitors have revolutionized antiretroviral therapy, they have also proven to be the most challenging agents for pediatric implementation. Because these agents are water-insoluble, it has been very difficult to produce palatable pediatric formulations. Additionally, the substances possess a high level of pharmacokinetic variability across age groups; therefore, it is

important to determine the appropriate dosage of these drugs for children of various ages, particularly for young infants, in whom pharmacokinetic variability is the greatest.

PACTG 338 was the first randomized pediatric study to compare dual-nucleoside analogue treatment (ZDV and lamivudine), to dual- or triple-drug regimens that included the protease inhibitor ritonavir, in a population of 298 clinically stable children with prior antiretroviral therapy. The study showed that the ritonavir-containing arms were superior in achieving virologic suppression and provided important observations on the tolerability of protease inhibitors in children. Another study, which evaluated combination therapy with the protease inhibitor indinavir and two nucleosides, found a good virologic effect, but a higher incidence of nephrolithiasis associated with using this therapy in children than was observed in adults. PACTG 1013 is pursuing further evaluation of a lower dose of indinavir in combination with low-dose ritonavir as a "pharmacologic booster."

PACTG 377, a randomized, controlled trial that evaluated combination therapies with three or more drugs with respect to their ability to suppress plasma HIV RNA, included 181 clinically stable children, who had previously received treatment without protease inhibitors. Children received one of four regimens, each containing stavudine, and either nevirapine plus ritonavir, lamivudine plus nelfinavir, nevirapine plus nelfinavir, or lamivudine plus nevirapine and nelfinavir. Approximately one-half of the children sustained a virologic response with HIV RNA levels below detectable limits at 24 weeks of treatment. More than one-fourth of children who received nevirapine experienced a rash. In a subset of 12 children, researchers evaluated the use of a twice-daily (rather than three times daily) nelfinavir-dosing regimen, together with stavudine and lamivudine; nearly two-thirds of the children experienced a sustained virologic response with HIV RNA levels below detectable limits at 24 weeks of treatment. All regimens were similar in their drug activity, but treatment with the four-drug regimen offered more durable viral suppression.

New Agents for Immune-Based Anti-HIV Therapy in Children

A Phase I/II study of a recombinant, $CD4^+$-containing, immunoglobulin-molecule recombinant CD4-IgG2 was studied in HIV-infected children by PAMAB-supported researchers. This agent is under development as a target for HIV virions that might otherwise infect patient $CD4^+$ cells, to reduce HIV levels and prevent infection of new cells. The safety, tolerability, and effect of recombinant CD4-IgG2 on HIV RNA levels were evaluated in a study that used single and multiple intravenous infusions; six children received four, 10 mg/kg doses of recombinant CD4-IgG2 weekly. Overall, the treatment was well tolerated. Four of the six children receiving multiple infusions showed a five-fold decrease in HIV RNA levels. Three children sustained reductions in HIV RNA levels at 14 days after treatment. After 28 days, peak HIV levels were reduced in all six children. Recombinant CD4-IgG2 seemed capable of reducing HIV burden in infected children.

ADOLESCENTS AND HIV INFECTION

The REACH component of AMHARN had a number of scientific objectives, including: examining the manifestations and progression of HIV infection in teens who were infected as teens, through sex or injecting drug behavior; exploring the immunologic profile in HIV-infected youth, while establishing normative immunologic data in sexually active, uninfected adolescents; and investigating sexually transmitted infection (STI) co-morbidity, particularly for HPV.

Researchers also collected considerable behavioral data to give context to the biomedical measures. Descriptions of the behavioral characteristics of the AMHARN subject population included contraception use; pregnancy rates; disclosure of HIV status to parents or partners; linkage between alcohol/drug use, depression, and sexual risk-taking; characteristics of sexual partners; condom use; douching practices; the association between among perceived health, clinical status, and decisions about initiating HAART, and with adherence to HAART; barriers to drug adherence; and HIV testing behaviors among youth.

Laboratory and clinical measures were also evaluated in AMHARN, including stimulated cytokine production; urine/cervical samples by ligase chain reaction for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*; comparison of antigen performance in eliciting delayed type hypersensitivity; urinary drug levels compared to ACASI self-report to obtain drug use data; performance and cost comparison of cervicography to cytology in detecting squamous intraepithelial lesions; general dietary intake, including the biochemical levels of vitamins, micronutrients, and antioxidants, as well as the relationship of these biochemical levels to HIV disease progression and measures of inflammation and oxidative damage; and body composition in relation to the National Health and Nutrition and Examination Study, or NHANES data.

HIV Disease Progression

At study entry, 16 percent of the females and 18 percent of the males enrolled in REACH had a diagnosis of AIDS; 85 percent of these diagnoses were based on $CD4^+$ T-cell count criterion alone. During the course of the study, eight subjects died (two related to metabolic complications of antiretroviral therapy), for observed death rates of 0.5 per 100 person-years in males, and 1.1 per 100 person-years in females.

In comparing the relationship between $CD4^+$ cell counts and HIV plasma viral load of the youth in the REACH Study to the same measures in cohort studies of adult males, the youth were found to exhibit different viral dynamics of $CD4^+$ T-cell depletion. Quantitative HIV-1 RNA viral load showed no association with the rate of $CD4^+$ T-cell loss in the REACH cohort, although absolute $CD8^+CD38^+$ T- cell counts at the start of the assessment period did show an association. This study yielded results consistent with other data, which indicate that higher $CD8^+CD38^+$ T-cells numbers predict HIV disease progression. The research also extends these associations to include predominantly female, minority youth; further, HIV RNA levels were not associated with $CD4^+$ T-cell decline in previous studies of racial-minority adult populations. These findings support the potential need for re-evaluation of HIV therapeutic guidelines based on demographic characteristics.

By genotyping the reverse transcriptase (RT) and protease genes of HIV in repository plasma samples of therapy-naïve youth, researchers evaluated community acquisition of drug-resistant HIV strains. The samples, obtained from 1996 to 1997, demonstrated genotypic mutations in the RT gene associated with drug resistance in four of 92 youth (4.3 percent), including one youth who had HIV with multiple resistance mutations. This result contrasts with an 8.0 percent rate of major genotypic drug resistance mutations detected among newly infected adults in 10 cities in North America between 1995 and 1998.

Researchers also examined REACH subjects for associations with early host-virus equilibration by studying the genotypes of cellular chemokine co-receptors (CCR). Among the major CCR 2 – CCR 5 haplotypes/genotypes in chronically infected and predominantly African American adolescents, only the E/E genotype was associated with viral load and early host-virus equilibration. The relationship between host genetic profiles and virologic and immunologic control of HIV infection in adolescents HLA class I and CCR alleles and haplotypes were determined using polymerase chain reaction-based techniques. These genetic profiles remained associated with mean $\log_{10}$ HIV RNA levels, even after adjustment for differences in gender, race, and history of antiretroviral therapy, which supports the need for further studies and consideration of selected genetic profiling in clinical management of HIV-infected subjects.

Immunology

Immunology commanded considerable attention in REACH because its related objectives were two-fold: (1) establish normative data in uninfected adolescents as comparator data on which efficacy interventions could be monitored; and (2) examine the impact of HIV infection on a developing immune system in the context of sexual maturation. The prevalence of anergy was correlated with $CD4^+$ T-cell count; youth with $CD4^+$ T-cell counts of 0-199/mm^3 were 6.7 times more likely to have anergy compared with those whose counts were 500/mm^3 or greater. The overall prevalence of anergy (11 percent) was low compared to data from older infected cohorts, which likely resulted from a healthier population and better-performing antigen in the REACH study. A study of response to hepatitis B virus (HBV) vaccination in HIV-infected youth identified an association of poor vaccine immune response that correlated only with $CD8^+/CD38^+/HLA\text{-}DR^+$ lymphocytes. Interestingly, a poor HBV vaccine response rate in the prospective cohort of HIV-uninfected adolescents was noted, suggesting that HBV vaccination doses may not have been optimized for older adolescents.

REACH also examined peripheral blood mononuclear cell markers in antiretroviral therapy-naïve, HIV-infected and high-risk seronegative adolescents. Markers were similar to those in other populations, but the observation of increased naïve $CD8^+$ T-cells in HIV-infected adolescents was novel, suggesting a greater thymic capacity in the adolescent population than in adults. Longitudinal examination of lymphocyte subset measures underscored the significant role of gender as the characteristic most frequently associated with differences. Females had higher total $CD4^+$ T-cell and memory $CD4^+$ T-cell counts, but lower $CD16^+$ T-cell counts than males.

T-cell receptor V-beta repertoire was determined in a limited number of antiretroviral-naïve, HIV-infected adolescents to assess the extent of damage to $CD4^+$ and $CD8^+$ T-cell compartments. Perturbations in the $CD8^+$ T-cell compartment were more profound when

compared to the $CD4^+$ T-cell compartment, but were not correlated with any other T-cell markers or viral load. Perturbations in the $CD4^+$ T-cell compartment correlated with total and naïve $CD4^+$ T-cell counts, as well as with $CD4^+$ recent thymic emigrant cells (as indicated by detection of T-cell receptor rearrangement excision circles [TRECs], which provide a measure of thymic activity), which indicates a profound effect on the $CD4^+$ T-cell compartment even though the youth were relatively early in the progression of their HIV disease.

The suggestion that HIV-infected adolescents have greater immunologic reserve has been pursued in studies of proliferation rate and number for various immune cell subsets. While naïve $CD4^+$ T-cells had a low rate of proliferation, proliferation of naïve $CD8^+$ T-cells was higher than previously demonstrated in adults, supporting the theory of adolescent ability to regenerate and/or expand this subset. Among uninfected REACH youth, TREC values, which provide a measure of thymic activity, remained stable in a longitudinal examination. $CD4^+$ and $CD8^+$ TRECs were not significantly different between HIV-infected and HIV-uninfected youth, demonstrating that HIV infection does not uniformly result in accelerated thymic involution.

As part of the collaborative DAIDS/NIAID-supported AIDS vaccine initiative, HIV-1 specific immune responses and epitope mapping to the five main HIV Clade B peptides were evaluated in the REACH cohort, composed primarily of female minority youth. The HIV-specific T-cell response, as measured by the Elispot assay, generally targeted the HIV peptides previously reported for Caucasian cohorts; however, a small but notable subset (12 percent) of the targeted peptides were novel. Furthermore, for previously reported reactive peptides, the HLA genotypes of the subjects often lacked the major histocompatability complex (MHC) class I allele reported to restrict the epitope, suggesting the use of alternative MHC class I proteins to present the same epitope.

These studies of HIV-specific responses were further refined to identify HLA-restricted and optimized $CD8^+$ cytotoxic T-cell responses. Researchers derived 24 HIV-specific $CD8^+$ T-cell lines of varying specificities from 12 individuals. Eight MHC class I restricted epitopes were previously described, another eight were restricted by MHC class I alleles not previously associated with these epitopes, and eight epitopes had not been described previously. The majority of epitopes (67 percent) were restricted by alleles found more frequently in African American or Hispanic populations. When tested further, the majority of these new epitopes were able to stimulate HIV-specific $CD8^+$ T-cell responses among persons of differing racial backgrounds. These immune response and immunogenetic data generated in racial groups in the United States that are now at the highest risk of HIV infection have added substantially to the national database and have provided substantial insights for vaccine development.

Co-Morbidities

High STI rates were observed in the REACH populations; for example, gonorrhea rates were 9.6 percent and 7.4 percent in HIV-infected and HIV-uninfected females, respectively, and were 7.9 percent and 6.9 percent in HIV-infected and HIV-uninfected males, respectively. The high rates of other STIs in these HIV-infected and HIV-uninfected adolescents underscored the sexual risk-taking behaviors in this population.

HPV and HBV were the most significant co-morbidities identified. Cervical HPV infections were identified in 77.4 percent of the HIV-infected females and 54.5 percent of the uninfected females at baseline. Infections with high-risk HPV types accounted for most of the differences between HIV-infected and uninfected youth. Anal HPV was detected in 31 percent of the 348 youth who had assessable anal samples; anal HPV was more common among males than females. Seroprevalence of HBV at baseline in the HIV-infected subjects was 24 percent. Among these HBV and HIV dually infected youth, 21 percent had evidence of active HBV infections, 15 percent of females and 36 percent of males. The seroprevalence of hepatitis C virus was 1.6 percent in the whole cohort at baseline, with no difference between HIV-infected and uninfected youth, and no association with intravenous drug or needle use.

WOMEN AND HIV

Highlights of selected investigations from the PAMAB-co-sponsored WIHS, WITS, and AACTG efforts are summarized below.

Natural History/Disease Progression

WIHS has contributed greatly to the understanding of the natural history of HIV disease in women, the response to therapy, the differences in disease parameters between men and women, and the causes of death in HIV-infected women. In the pre-HAART era, WIHS demonstrated that survival time and time to development of AIDS were similar over three years of follow up among women with $CD4^+$ lymphocyte counts between 200/mm^3 and 349/mm^3, and over 350 cells/mm^3. Subsequent data showed that the rate of AIDS development and death was similar between these two groups up to four years after initiation of HAART, although further follow up is required because the death rate may be beginning to diverge. Analysis of the causes of death among women enrolled in WIHS determined that 20 percent of deaths among HIV-infected women were not directly related to HIV, but were attributable to liver failure, drug overdose, malignancies not associated with HIV, cardiac events, and trauma, which suggests important additional areas for intervention.

WIHS also demonstrated that HIV RNA levels in women compared to men, and in non-whites compared to Caucasians, were lower at a given $CD4^+$ lymphocyte count; these characteristics persisted until these counts dropped below 200 cells/mm^3. Additional markers of disease progression that are more easily determined, such as serum albumin and anergy, were evaluated by WIHS and were shown to be independent predictors of disease progression; these markers may have utility in resource-limited countries. WITS analyses evaluated the impact of drug use and subsequent pregnancies on HIV disease progression; neither was found to negatively impact HIV RNA levels, $CD4^+$ lymphocyte changes, or clinical disease progression.

Use of and Response to Highly Active Antiretroviral Therapy (HAART)

WIHS provided population-based data that documented a decreasing rate of new AIDS diagnoses and deaths as the rate of HAART use increased, among a predominantly minority and disadvantaged group of women. In addition, WIHS noted the large number of antiretroviral regimens used (more than 160 unique regimens among 1,056 women on HAART), and the high frequency of switching or discontinuing therapy, with a median time of only eight months from

initiation of HAART until regimen change. Evaluation of antiretroviral therapy use by women who became pregnant while enrolled in WIHS demonstrated that, over time, the patterns of therapy use in pregnant women had become similar to those of non-pregnant women, with similar proportions of both groups receiving HAART.

Hormonal Influences and Genital Tract HIV

WIHS investigators have independently, and in collaboration with other studies, such as the CDC-funded HIV Epidemiologic Research Study and the NICHD- and NIAID-funded Women's HIV Study, evaluated the effects of HIV on the menstrual cycle, the impact of hormonal changes that occur during the menstrual cycle on systemic and genital HIV and cytokines, and the interaction of the genital milieu and HIV detection. Analysis found similar menstrual cycle characteristics between HIV-infected and HIV-uninfected women, except for an increase in variability of cycle length among HIV-infected women who had very low $CD4^+$ lymphocyte counts. HIV-infected women were found to more frequently have genital ulcerations, warts, and candidiasis, compared to HIV-uninfected women, who were more likely to have bacterial and protozoal infections.

WIHS investigators developed and validated methods for detecting HIV infection in the female genital tract. Although plasma HIV RNA levels were the key predictor of HIV detection in the genital tract, HIV was detected in the genital tracts of some women who had undetectable plasma HIV RNA. Plasma cytokine levels and $CD4^+$ and $CD8^+$ lymphocyte counts did not vary over the menstrual cycle, whereas vaginal levels of several cytokines, MIP- *beta*, RANTES, and TGF-*beta*, and HIV were elevated during menses, compared to other portions of the menstrual cycle. The effects, if any, of the change in hormone levels during the course of the menstrual cycle on plasma and genital tract HIV levels remains controversial, with variable effects reported. Several studies have suggested increased detection and levels of HIV in the genital tract among women with bacterial vaginosis; WIHS investigators are working to further characterize the factors responsible for this observation, and to understand the impact of bacterial vaginosis treatment on HIV detection in the genital tract.

Another important issue that WIHS shed light on is the potential effect of endogenous or exogenous hormones in women on the metabolism of antiretroviral drugs. The NICHD has co-supported two studies on the effects of contraceptive hormones on the pharmacokinetics of selected antiretroviral agents: AACTG 317, which is evaluating the effect of oral and injectable contraceptives (norethindrone/ethinyl estradiol, medroxyprogesterone acetate) and gender on plasma and intracellular ZDV pharmacokinetics; and AACTG 5093, which is evaluating pharmacokinetic interactions between depomedroxyprogesterone acetate (Depo-Provera) and selected protease inhibitor and non-nucleoside RT inhibitor therapies. Data from AACTG 317 are being analyzed, while AACTG 5093 is ongoing.

HPV and Genital Neoplasia

The WIHS, as the largest, ongoing, natural history study of HIV infection in women, has played a key role in understanding the interaction of HIV infection and HPV infection, the primary factor in genital and anal neoplasia development. Important findings to date include: the increased prevalence and incidence of genital and anal HPV infection, warts, and cervical cytologic abnormalities among HIV-infected women, with higher rates noted among women

with lower $CD4^+$ lymphocyte counts; a relatively uncommon occurrence of high-grade cervical dysplasia among HIV-infected women; and the potential for HAART to induce regression of HPV-related cervical abnormalities. A substudy of WIHS evaluated the mucosal immune response to high-grade cervical dysplasia among HIV-infected women compared to HIV-uninfected women; findings indicated that, among the 40 percent of HIV-infected women with a novel type of lymphoid follicle consisting predominantly of $CD8^+$ T-cells (compared to 0 percent in HIV-uninfected women), the recurrence risk was significantly higher one year after treatment. Further evaluation of the impact of HAART regimens on genital HPV-related abnormalities is required and is ongoing in WIHS and AACTG 5029, co-sponsored by the NICHD. NICHD-funded sites have also enrolled HIV-infected women into other AACTG studies that are evaluating novel regimens for treatment or prevention of cervical dysplasia: AACTG protocol 200 demonstrated a reduced risk of recurrent dysplasia with use of intravaginal 5-fluorouracil after ablative therapy of high-grade cervical lesions; and AACTG 293 evaluated the efficacy of oral isotretinoin for treatment of low-grade, cervical lesions among HIV-infected women, but no efficacy was observed.

Psychosocial/Behavioral

Several analyses have explored psychosocial issues and their impact on medication adherence and study retention among women enrolled in the WIHS. Two-thirds of the women enrolled in WIHS had a history of domestic violence, while more than one-fourth had a history of childhood sexual abuse; proportions of both these characteristics were similar among HIV-infected and HIV-uninfected women. Both domestic violence and childhood sexual abuse were associated with an increased risk of illicit drug use and STIs other than HIV. Assessment for depression revealed similarly high rates in both HIV-infected and uninfected women; education level, lower income, drug or alcohol use, domestic abuse, and fewer social supports were associated with depression in both groups. Factors associated with retention in WIHS included older age, African American heritage, stable housing, being HIV-infected, and past experience with studies of HIV. Among HIV-infected women, self-reported adherence to antiretroviral therapy was associated with increased age, lack of cocaine or heroin use, health perception score, and having an undetectable HIV RNA level. Assessment of sexual behavior revealed that HIV-infected women were more likely than HIV-uninfected women to use condoms (63 percent versus 28 percent, respectively), but risky sexual behavior remained common in both groups, and even increased for some women after HAART initiation.

Other Manifestations of HIV Infection

WIHS is actively studying many other manifestations of HIV infection in women. The WIHS Oral Working Group described the frequency of oral mucosal lesions, warts, and salivary gland dysfunction among HIV-infected women, compared to uninfected women; it is now evaluating the impact of HAART on oral complications. Skin manifestations including folliculitis, seborrheic dermatitis, herpes zoster, and onychomycosis were more common among HIV-infected women compared to uninfected women, and increased with $CD4^+$ lymphocyte counts below 50 cells/mm^3. Concomitant viral infections, such as herpes simplex, human herpes virus-8 (HHV8), and human T-lymphotropic virus types I and II were also described. For example, in WIHS, HHV8 antibodies were detected among 4.1 percent of women; and in WITS, the detection rate was 5.3 percent. In both studies, HHV8 seropositivity was associated with previous STIs, injection drug use, and site of enrollment.

A large focus of the ongoing study is evaluating the interactions of hepatitis C virus infection and HIV infection, and the impact of each on the treatment of the other. Additionally, HIV-resistance testing will be correlated with limited pharmacokinetic sampling in women receiving antiretroviral therapy, and with treatment outcome. As HAART use has increased and metabolic abnormalities related to long-term HIV infection and therapy have been identified, WIHS has added detailed evaluation of body composition, lipid levels, cardiac risk factors, bone changes, and other metabolic parameters. Inclusion of the HIV-uninfected cohort in WIHS will allow investigators to differentiate complications related to HIV infection and antiretroviral therapy, from those related to aging and poverty, in this disadvantaged, predominantly minority cohort.

FUTURE DIRECTIONS

Since the Branch's last report to the NACHHD Council, it has significantly modified its portfolio of HIV/AIDS research, while maintaining a diverse research program that includes unsolicited and solicited investigator-initiated grants, as well as longitudinal, epidemiologic studies and treatment/prevention trials funded through cooperative agreements and contracts.

Based on the scientific findings that have resulted from the observational studies of HIV-infected youth in AMHARN, adolescent research funded by PAMAB has evolved to encompass interventional research through the ATN that includes primary prevention research, such as HIV vaccine trials, and clinical management of HIV-infected youth, such as evaluation of novel drug regimens, drug adherence, and risk reduction. This research will be conducted in collaboration with other networks, such as the PACTG and HVTN.

Additionally, in recognition of the decline in perinatal HIV transmission in the United States due to the development of highly effective preventive interventions, and the continuing and expanding HIV epidemic among women and children in resource-limited settings, PAMAB has dramatically increased its funding of international research. This expansion is made possible through a variety of mechanisms, including investigator-initiated, international clinical trials, co-funding of the HPTN and a new innovative collaboration with the CDC, and through funding reallocations and special OAR funding additions to the NICHD domestic, and now international, Pediatric and Perinatal HIV Studies Network.

Over the next five years, the Branch plans to:

- Expand its portfolio of investigator-initiated grant research, with a focus on international research, and on the pathogenesis and prevention of breast milk HIV transmission.
- Continue to support several domestic, longitudinal, epidemiologic studies in HIV-infected pregnant women, their infants, and HIV-infected non-pregnant women, with a focus on changes in the natural history of HIV disease in an era of HAART, and on the short- and long-term effects of such therapies on infected individuals and the child with *in utero* exposure.

- Maintain the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network and its successful collaboration with the NIAID-funded PACTG to evaluate interventions that reduce perinatal transmission and treat HIV infection and its associated complications in infants, children, adolescents, and women.
- Further expand the NICHD Domestic and International Pediatric and Perinatal HIV Studies Network to include additional international clinical trials sites in resource-limited settings, particularly in the Caribbean, where there are currently few research activities being funded.
- Continue to develop innovative studies that support infrastructure development and clinical trials training in resource-limited settings, through studies such as NISDI and the Perinatal HIV Transmission Prevention Program in India.
- Continue collaborating on international perinatal prevention trials with the HPTN, and with the CDC, a new partner in this endeavor.

FIGURES

FIGURE 1: PAMAB FUNDING FOR FISCAL YEARS 1999-2002

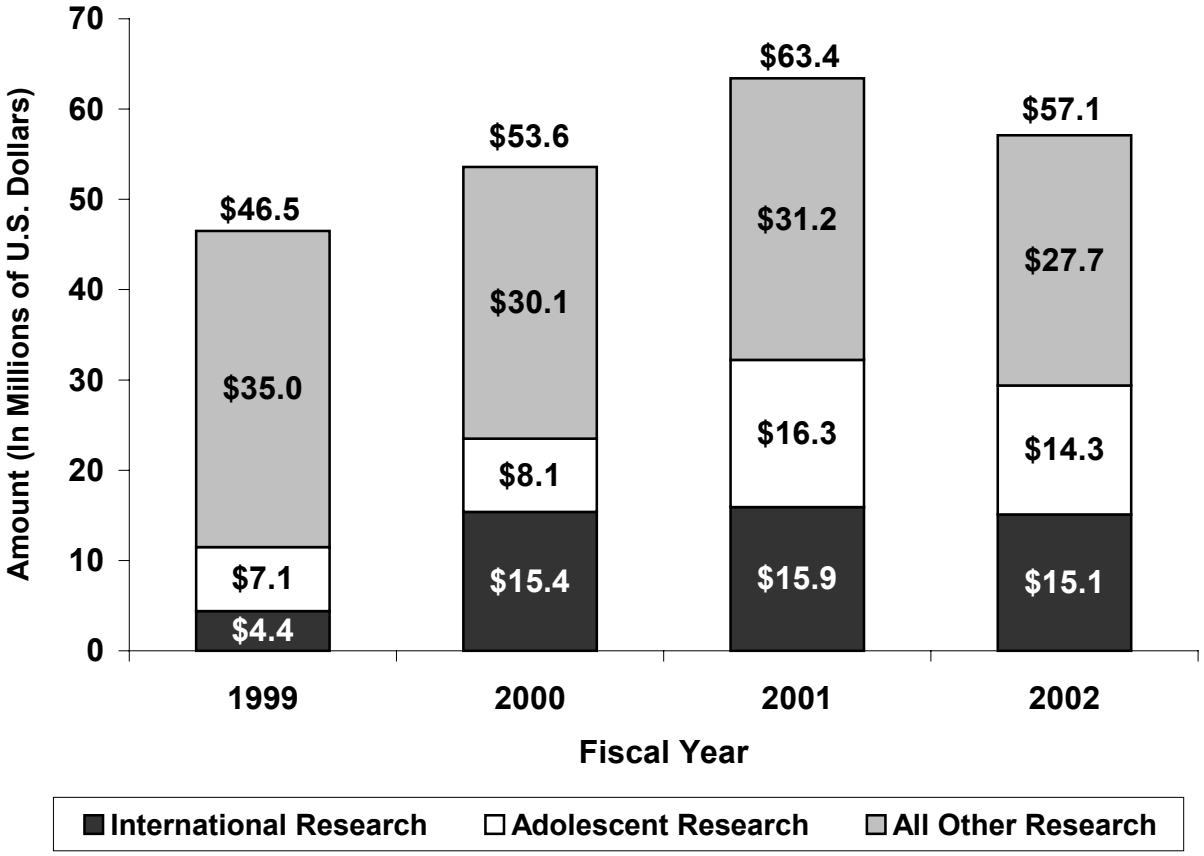


FIGURE 2: PAMAB FUNDING FOR FISCAL YEARS 1999-2002, COMPONENTS OF INTERNATIONAL RESEARCH FUNDS

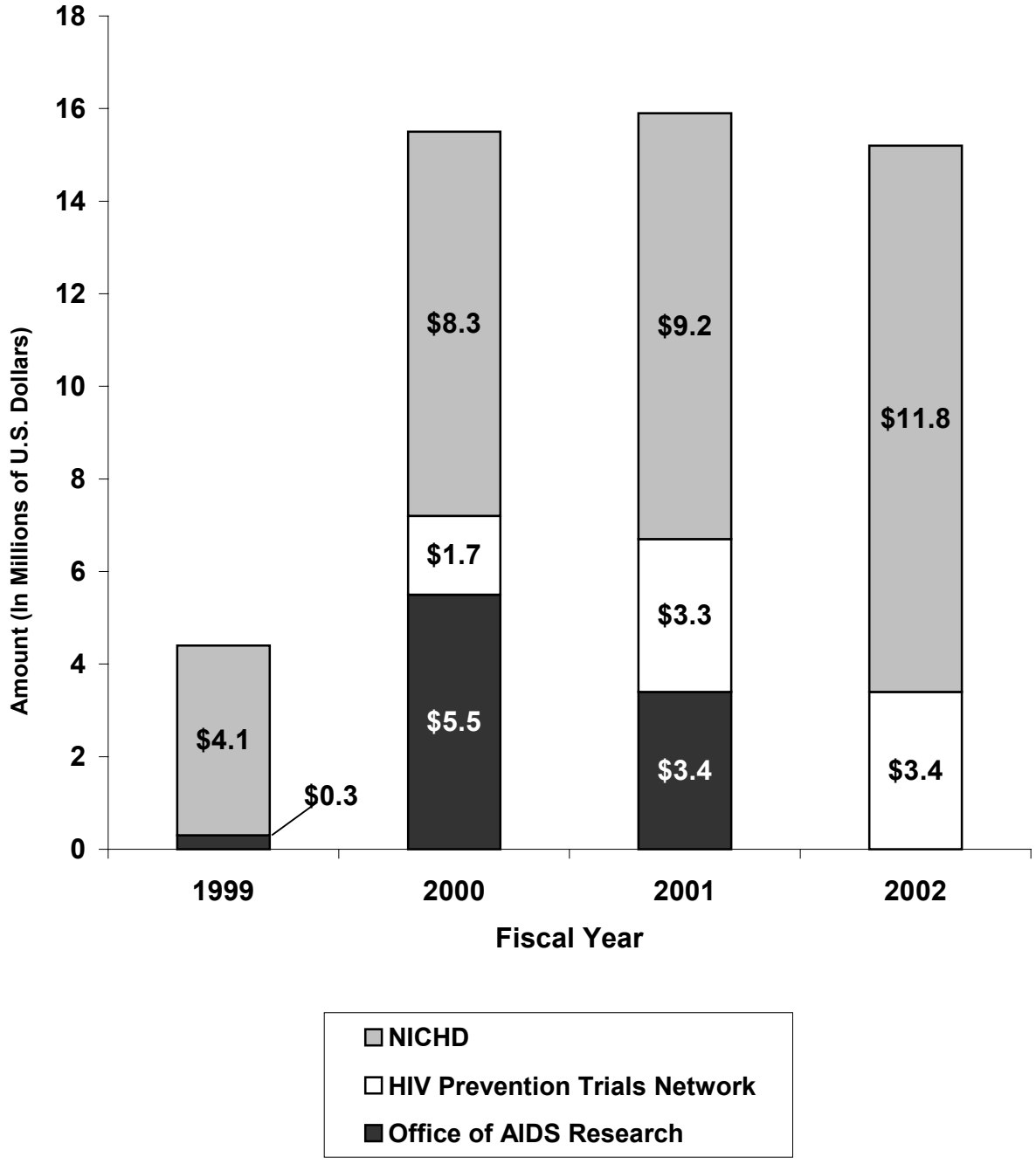
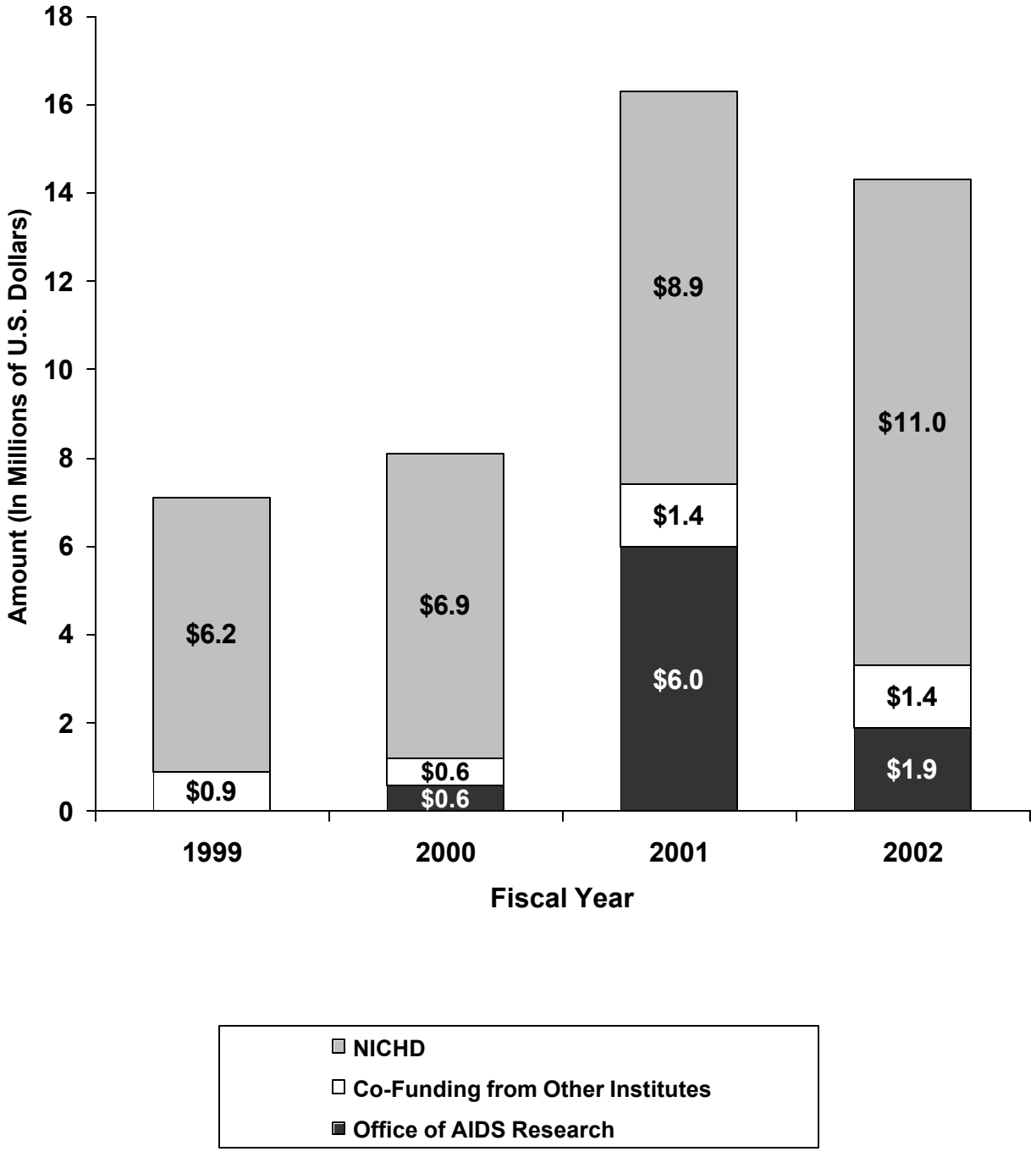


FIGURE 3: PAMAB FUNDING FOR FISCAL YEARS 1999-2002, COMPONENTS OF ADOLESCENT RESEARCH FUNDS



APPENDIX A: PAMAB PERSONNEL

In 2002, PAMAB received the Department of Health and Human Services (DHHS) Secretary's Award for Distinguished Service for its efforts in preventing mother-to-child HIV transmission, and in conducting studies leading to the approval of new treatments for HIV-infected infants, children, adolescents, and pregnant women.

Lynne M. Mofenson, M.D., is an infectious disease specialist and board-certified pediatrician. Dr. Mofenson received her medical degree with honors (Alpha Omega Alpha) from Albert Einstein College of Medicine in 1977, completed a pediatric residency at Boston Children's Hospital, and finished a pediatric chief residency and joint adult/pediatric infectious disease fellowship at the University of Massachusetts Medical School. Prior to coming to the National Institutes of Health (NIH), she spent five years as assistant commissioner for public health in Massachusetts, where she directed the Communicable Disease Program for the Massachusetts Department of Public Health. Before that position, she spent three years in the private practice of adult and pediatric infectious diseases and pediatrics in Massachusetts. Dr. Mofenson came to the NIH in 1989, as associate branch chief for clinical research in PAMAB and became chief of PAMAB in December 2001. Dr. Mofenson is responsible for program planning and for the development and scientific direction of research studies and clinical trials in domestic and international pediatric, adolescent, and maternal HIV infection, disease, and AIDS. She is project officer for the multi-site NICHD Domestic and International Pediatric and Perinatal HIV Clinical Studies Network. Dr. Mofenson has published extensively on treatment of HIV infection in children and women, and on prevention of perinatal HIV transmission; she is involved in many national and international policy and guideline groups related to HIV infection in children and women, and serves as a consultant to UNAIDS/WHO on issues related to antiretroviral treatment and care of HIV-infected women and their children. Dr. Mofenson received the DHHS Secretary's Award for Distinguished Service in 1997, 1999, and 2002.

John H. Moye, M.D., is a pediatrician and former state public health official who joined the Branch in 1990, as a physician scientist and medical officer. His background is in clinical and laboratory medicine and public health, with an emphasis on the prevention and control of communicable and chronic diseases, including sexually transmitted diseases and HIV/AIDS. He is a 1982 graduate of the University of Massachusetts Medical School and trained in pediatrics at the Boston City Hospital from 1982 to 1986, where he served as chief resident and as senior attending physician in pediatric emergency services from 1986 to 1990. He has been an HIV/AIDS consultant for state departments of social services, corrections, youth services, and education. He has been a member of the Massachusetts Governor's Task Force on AIDS, the New England Governors Conference Task Force on AIDS and Intravenous Drug Use, and the U.S. Public Health Service Surgeon General's Panel on Women, Adolescents, and Children with HIV Disease and AIDS. His areas of activity for PAMAB include the NICHD Domestic and International Pediatric and Perinatal HIV Clinical Studies Network, the PACTG, and WITS, where he chairs the clinical working group; virology and immunology research; laboratory quality assurance; growth and nutrition; and international research initiatives.

Robert P. Nugent, Ph.D., joined PAMAB in 1988, after 12 years in the Division of Epidemiology, Statistics, and Prevention Research (DESPR) at the NICHD. Dr. Nugent received his master of public health degree from the University of California at Los Angeles, and his Ph.D. from Johns Hopkins University School of Hygiene and Public Health, with a focus on infectious disease epidemiology. Dr. Nugent has served as the associate branch chief for epidemiologic and biostatistical research since 1989. He is responsible for WITS, funded by both the NICHD and NIAID, and serves on the executive committee, steering committee, and publications committee for the study. He also serves as the administrative coordinator of WIHS and the ATN.

Jennifer S. Read, M.D., M.S., M.P.H., D.T.M. & H., board-certified in pediatrics and in pediatric infectious diseases, joined the NICHD in 1990. She received her undergraduate and graduate degrees in biological sciences from Stanford University. Subsequently, she graduated from medical school at the University of Arkansas for Medical Sciences and completed her residency in pediatrics at the University of Michigan. She received clinical fellowship training in pediatric infectious diseases at the Johns Hopkins University and the University of Michigan and received advanced training in tropical medicine at the London School of Hygiene and Tropical Medicine. She began a U.S. Public Health Service Epidemiology Training Program Fellowship at the NICHD in 1990, received a master's degree in public health from the Harvard University School of Public Health in 1991, and worked as a staff fellow and subsequently a senior staff fellow in DESPR at the NICHD, before joining PAMAB in 1995. Since then, Dr. Read has contributed to the development, execution, and analysis of domestic and international clinical trials and other epidemiological studies related to pediatric HIV infection and prevention of mother-to-child transmission. Her research has focused on the role of cesarean section in the prevention of mother-to-child transmission and, more recently, on the prevention of such transmission among mothers who breastfeed; she developed and led two international collaborations that resulted in individual patient data meta-analyses in these areas. In addition, she has developed an operational research project regarding prevention of mother-to-child transmission of HIV in rural India, and, as the principal investigator for the perinatal protocol of NISDI, is collaborating with in-country investigators on description and analysis of mother-to-child transmission of HIV in Latin America and the Caribbean. She has received the NIH Director's Award (1999) and the Pediatric Infectious Diseases Society Young Investigator Award (2001).

Audrey Smith Rogers, Ph.D., did her undergraduate study in nursing at the University of Maryland. She pursued graduate study at the University of North Carolina at Chapel Hill and received a master's degree in clinical pharmacy and public health, and a doctoral degree in epidemiology. She did postdoctoral study in pharmacoepidemiology at the University of North Carolina and at the Johns Hopkins University School of Medicine. Dr. Rogers was on staff at the Johns Hopkins Pharmacoepidemiology Unit from 1985 to 1988, and was involved in various post marketing drug surveillance projects. From 1988 to 1992, she was the chief of AIDS epidemiology for the Maryland State Department of Health and Mental Hygiene. She joined PAMAB in 1992. She is a member of the adolescent scientific committee of the PACTG. She was the science officer for the REACH Project and AMHARN from 1994 to 2001, an observational study of a medically managed population of HIV-positive youth. She is also the science officer for the ATN. Dr. Rogers is active in the Society for Adolescent Medicine,

particularly in the development of guidelines for adolescent participation in and the ethical conduct of research. She is a reviewer for the *Archives of Pediatric and Adolescent Medicine* and the *Journal of Adolescent Health*, on whose editorial board she serves. Dr. Rogers has received the 1996 Ryan White Youth Service Award from Metro Teen AIDS in Washington D.C., and the 2002 NIH Director's Award for her work in adolescent HIV infection.

Leslie K. Serchuck, M.D., M.A., is an infectious disease specialist and board-certified pediatrician. She received her graduate degree in counseling psychology and her medical degree from Boston University School of Medicine. Her residency and fellowship training in infectious diseases were at Boston City Hospital (now Boston Medical Center). Following her fellowship, she worked at the HIV and AIDS Malignancy Intramural Branch at the NCI for five years before joining PAMAB as a medical officer in January 2001. She is currently responsible for collaboration with the PACTG in the design and analysis of clinical trials evaluating pediatric HIV therapies. She is an active member of the leadership group of the ATN. As the principal investigator for the pediatric protocol of NISDI, she is collaborating with in-country investigators on a prospective, observational study of HIV-exposed and infected infants, children, and adolescents at six new (and six existing) international sites in Latin America, which began enrollment in September 2002. In addition, since 1998, she has played an important and active role on the Clinical Center Bioethics Committee at the NIH.

D. Heather Watts, M.D., joined the PAMAB in July 1998, from the University of Washington, where she was an associate professor of obstetrics and gynecology and adjunct associate professor in health services, as well as medical director for obstetrics for the Seattle King County Department of Public Health. She graduated from the Pennsylvania State University and Jefferson Medical College, completed her residency in obstetrics and gynecology at Thomas Jefferson University Hospital, and finished her fellowship training in maternal-fetal medicine and infectious diseases at the University of Washington. Currently, Dr. Watts is participating in many collaborative efforts aimed at improving the health of HIV-infected women and preventing perinatal transmission of HIV. Dr. Watts is leading the NICHD-sponsored study of neonatal antiretroviral prophylaxis for prevention of transmission among infants born to untreated women in Brazil. She is an active participant on many PACTG trials aimed at reducing perinatal HIV transmission and providing optimal treatment for HIV-infected pregnant women. In addition, Dr. Watts serves on the Women's Health Committee and several women's health studies in the AACTG. She has chaired the mucosal/reproductive health working group, serves on the executive committee of WIHS, and participates in WITS. Dr. Watts serves on many U.S. Public Health Service guideline committees related to HIV and sexually transmitted disease in pregnant women and was recently elected secretary of the Infectious Disease Society for Obstetrics and Gynecology.

APPENDIX B: PAMAB STAFF ACTIVITIES

Lynne Mofenson

U.S. Public Health Service Guideline Committees

- Perinatal Treatment Guidelines (Executive Secretary)
- Pediatric Antiretroviral Treatment Guidelines
- Adult Antiretroviral Treatment Guidelines
- Prevention of Opportunistic Infections in HIV-1-Infected Persons
- Treatment of Opportunistic Infections in HIV-1-Infected Children (Executive Secretary)
- Recommendations for HIV Counseling and Voluntary Testing for Pregnant Women

National Institutes of Health

- Working Group to Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities (Co-Chair, Perinatal Working Group)
- Office of AIDS Research Therapeutics Committee

World Health Organization

- Guidelines for Antiretroviral Therapy in Resource-Limited Settings (Writing Group)
- Impact of HAART during Pregnancy and Breastfeeding on Mother-to-child Transmission and Maternal Health (Research Group)
- Meeting on Use of Nevirapine for Prevention of Mother-to-child Transmission of HIV Among Women of Unknown Serostatus (Consultant)
- Reference Guide on HIV-Related Care, Treatment, and Support of HIV-Infected Women of Reproductive Age and Their Children in Resource-Constrained Settings (Writing Committee)

Other Organizations

- Committee on Pediatric AIDS, American Academy of Pediatrics (NICHD liaison)
- Institute of Medicine Committee on Perinatal Transmission of HIV (NIH liaison)
- Elizabeth Glaser Pediatric AIDS Foundation Children's Research Fund Advisory Committee
- *Journal of the Acquired Immune Deficiency Syndromes* Editorial Board
- AIDScience Scientific Advisory Board
- The National Resource Center for AIDS Education and Training Center Faculty Reviewer

Jack Moye

U.S. Public Health Service Guideline Committee

- Health Resources and Services Administration HIV Guidelines for Nutrition Working Group

National Institutes of Health

- Office of AIDS Research Etiology and Pathogenesis Committee

Jennifer Read

- Ghent-International AIDS Society Working Group on HIV in Women and Children (Steering Committee)
- Committee on Pediatric AIDS, American Academy of Pediatrics (Member)
- Pediatric Infectious Disease Society liaison to the HIV Medicine Association of the Infectious Disease Society of America

Audrey Rogers

National Institutes of Health

- Working Group to Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities (Co-Chair, Adolescent Working Group)
- Office of AIDS Research Vaccine Committee and Racial/Ethnic Minority Committee

World Health Organization

- Guide to Management of HIV-Infected Youth (Writing Group)

Other Organizations

- *Journal of Adolescent Health* Editorial Board

Leslie Serchuck

U.S. Public Health Service Guideline Committees

- Pediatric Antiretroviral Treatment Guidelines
- Treatment of Opportunistic Infections in HIV-Infected Children

National Institutes of Health

- Clinical Bioethics Committee (Clinical Center)
- Clinical Research Advisory Committee (NICHD)
- National Eye Institute Institutional Review Board (Adjunct *Ad Hoc* Member)
- Office of AIDS Research Natural History/Epidemiology Committee and International Committee

Heather Watts

U.S. Public Health Service Guideline Committees

- Perinatal Treatment Guidelines
- Sexually Transmitted Diseases Treatment Guidelines
- Prevention of Opportunistic Infections in HIV-1-infected Persons
- Treatment of Opportunistic Infections in HIV-1-infected Persons

National Institutes of Health

- Transinstitute Microbicide Working Group

Other Organizations

- American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women
- Infectious Disease Society for Obstetrics and Gynecology: Secretary and Program Chair
- Antiretroviral Pregnancy Registry (NICHD Liaison)

APPENDIX C: PUBLICATIONS BY PAMAB PERSONNEL: 1999-2002

PUBLICATIONS: JOURNALS

Culnane M, Fowler MG, Lee SS, McSherry G, Brady M, O'Donnell K, **Mofenson L**, Gortmaker SL, Shapiro DE, Cunningham B, and Oleske J, for the PACTG and Protocol 219/076 Teams. Late effects of *in utero* exposure to zidovudine among uninfected infants born to HIV-infected women. *JAMA.* 1999;281:151-7.

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APPENDIX D: NICHD DOMESTIC AND INTERNATIONAL PEDIATRIC AND PERINATAL HIV STUDIES NETWORK CLINICAL SITES

DOMESTIC

- Children's Diagnostic and Treatment Center of South Florida, Fort Lauderdale, Florida
- Children's National Medical Center, Washington, DC
- Harlem Hospital Center, New York City, New York
- Howard University Hospital, Washington, DC
- Jacobi Medical Center (subsites at Montefiore Medical Center, Lincoln Hospital), Bronx, New York
- New York University Hospital, New York City, New York
- San Juan City Hospital, San Juan, Puerto Rico
- State University of New York Health Science Center at Brooklyn, Brooklyn, New York
- State University of New York Health Science Center at Stony Brook, Stony Brook, New York
- State University of New York Health Science Center at Syracuse, Syracuse, New York
- University of Colorado Health Sciences Center, Denver, Colorado
- University of Florida College of Medicine, Gainesville, Florida
- University of Florida Health Science Center, Jacksonville, Florida
- University of Illinois College of Medicine, Chicago, Illinois
- University of Rochester School of Medicine and Dentistry/Strong Memorial Hospital, Rochester, New York
- University of South Florida, Tampa, Florida
- University of Southern California Medical Center/Los Angeles County Hospital, Los Angeles, California
- University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
- University of Washington, Seattle, Washington
- Wayne State University, Detroit, Michigan
- Yale University School of Medicine, New Haven, Connecticut

International

- Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paolo, Ribeirao Preto, Brazil
- Hospital dos Servidores do Estado, Rio de Janeiro, Brazil
- Instituto de Infectologia Emilio Ribas, Sao Paulo, Brazil
- Servico de Doencas Infecciosas - HUCFF, Rio de Janeiro, Brazil
- Princess Margaret Hospital, Nassau, the Bahamas
- Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

APPENDIX E: ADOLESCENT MEDICINE TREATMENT NETWORK FOR HIV/AIDS INTERVENTIONS CLINICAL SITES

- Children's Diagnostic and Treatment Center of South Florida, Fort Lauderdale, Florida
- Children's Hospital, Boston, Massachusetts
- Children's Hospital, Los Angeles, California
- Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
- Children's Research Institute, Washington, DC
- Hektoen Institute for Medical Research (Cook County Hospital), Chicago, Illinois
- Montifiore Hospital, Bronx, New York
- Mount Sinai School of Medicine, New York, New York
- Tulane University of Louisiana, New Orleans, Louisiana
- University of California at San Diego, San Diego, California
- University of California at San Francisco, San Francisco, California
- University of Maryland, Baltimore, Maryland
- University of Miami, Miami, Florida
- University of South Florida, Tampa, Florida
- University of Puerto Rico Health Science, San Juan, Puerto Rico
- Scientific Leadership Coordinating Center at University of Alabama at Birmingham, Birmingham, Alabama